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The voice of the people—which one?

ONE of the unmistakeable trends of the 1970s has been for the question of risk—its measurement, perception and acceptance—to move progressively away from being a purely technological problem and towards the centre of the political stage. Scientists and technologists may have been able to come up with numerical values and probabilities and indeed as a result of their work immense strides have been made in raising safety standards. But a never-ending succession of accidents, major and minor, continues to remind us that the risks of a technological world, be they from unsafe drugs, faulty nuclear reactors, wrecked supertankers or whatever, come largely from human and institutional frailty and not from imperfect materials or inappropriate differential equations. Small wonder then that risk is now a political issue.

Many scientists and technologists are bitter about the way apparently technical issues have been taken over by social scientists, bureaucrats and politicians. It would be wrong totally to dismiss this bitterness as professional narrow-minded jealousy without giving some thought to whether an embittered profession will attract the ablest young people to it. Nevertheless, the problematical nature of the interaction of humans with technology, as controller as well as potential sufferer inevitably means that wider circles of opinion are now being sounded out, and that even wider circles may have to be consulted in the future. But what exactly does public participation in the handling of technological risk questions mean? This was one of the important issues raised at a recent seminar in Berlin organised by the European Economic Community and the European Committee on Research and Development (CERD).

If decisions are not simply to be handed down from remote technocratic elites, responsible only to themselves, it is all but inevitable that there will be dissension, some of it vigorous. And as Dorothy Nelkin of Cornell put it, "resolving conflicts is much like seeking 100% risk-free technology—hardly a feasible goal". What has to be done is that all sides must see that their case is at least taken into account by whoever makes the decision, and they must be satisfied that the choice of decision-maker and the form of inquiry does not prejudice the case. Apparently harmless criteria—yet it was striking how many unsatisfactory cases could be cited where the decision was a foregone conclusion or where objectors found themselves seriously hindered.

That said, however, a striking theme to emerge from the seminar was that objectors to technological developments on grounds of unreasonable risk should be smoked out on what they really stand for. This, it was suggested, could be done in two ways. First, they should be asked whether they were aware of the consequences of saying no to particular projects, and had thought them through as carefully as they had thought through their objections. Second, many objectors to technological projects do so not because they disapprove of one particular proposal at one particular place, but because such projects go against their total sense of values. In the words of Jerry Ravetz of Leeds "we must recognise that we can no longer follow the politics of 'economism', where quantitative differences can be negotiated between opposing sides; rather we must accept some features of the politics of 'ethnicity', where deep differences of values must be confronted and then used for the mutual education of both sides".

It is clear that there is absolutely no agreement about just how widely views on risk should be canvassed. When three out of four drivers, given a chance, will spurn the use of a seat-belt for no apparent reason whatever, it is obvious that thinking by the man-in-the-street about risk-taking is immensely complex, not to say irrational. So how do we represent—indeed who represents—this man-in-the-street, and is this element of irrationality to be despised or to be allowed for? The problem is that we may be in danger of replacing a technological elite by yet another elite which thinks it knows what the public wants or ought to want. The long-term answer, and this should be regarded as a long-term problem not just here for a few years, must surely lie in much more effective education at all levels in thinking about technology and risk. Few technologists are taught to think about social matters. Few social scientists are taught to think about technology in depth. It is here that progress must be made.

The European Economic Community could feel pleased with this seminar. It is a subject peculiarly appropriate to the community. Individual nations cannot at present muster the resources to take an omnidirectional view of the subject. Yet each is having to cope with a set of broadly similar problems in its own distinctive way. What more valuable than to let these varying patterns rub off on each other under EEC auspices. □



Anti-war movements—heading for a 60s revival?

David Dickson reports from California on how critics of US military policy are beginning to tap the grass-roots energy of the anti-nuclear movement

It might have become a formula for instant nostalgia. But when the film version of the 1960s anti-war musical *Hair* opened in California a few weeks ago, it was reviewed—and widely praised—at face value, with few claiming that its sentiments belonged to the previous decade. And taken with the success of two other anti-war films in last week's Oscar awards, the popularity of *Hair* suggests that these sentiments remain close to the surface.

In Washington, concern about the security of Middle East oil supplies is already generating the type of discussion about 'protecting natural interests' that preceded the military intervention in Vietnam. And a question now being debated on many campuses throughout the US is whether opposition to a growing military budget and to an increasingly hawkish administration is likely to coalesce into something comparable to the anti-war movements of the 1960s.

To judge from the situation in California, such a coalescence may not be too far away. At present, various groups are concentrating on a number of different objectives, some only distantly related to one another. But growing concern about US military policy in general—together with unease about nuclear energy in all its forms after the Harrisburg accident—are beginning to draw these groups together.

Some of the more recent events include:

- At the University of California's Berkeley campus, a senate policy committee has recommended that the university sever all links with its Lawrence Livermore and Los Alamos laboratories, claiming that the large proportion of the activities of the two laboratories devoted to weapons research make the involvement of the university—currently responsible for the management of each—"totally inappropriate".

- A number of Californian and anti-nuclear groups are expected to take part in demonstrations outside the university demanding that the laboratory's skills and resources be turned "totally towards peaceful research" as a way of putting the cap on the arms race.

- At Stanford University, a group of students is mounting a campaign to oppose legislation being discussed in Washington for revising the draft. One of the first speakers to address a

university meeting on the issue was David Harris, student president in 1966-67 who spent 20 months in prison for draft evasion.

- A number of requests has been received by the American Association for the Advancement of Science to place public discussion of the US military budget and its implications on the agenda of next year's annual meeting in San Francisco.

- A Berkeley group has published, through the Washington-based Institute for Policy Studies, a pamphlet on "resurgent militarism", claiming that "all struggles for social progress . . . must confront the new militarism", and that otherwise "the likelihood of nuclear war will surely increase".

Such concerns are by no means confined to the West Coast. At a national level, church and religious leaders have, in particular, put military spending at the top of their agenda of items of social concern, both on a national and an international basis.

Similarly anti-nuclear groups, once concerned primarily with the safety parameters of energy policies, are making the links to military policy. "If you've done your homework you know you cannot separate the two issues" says Marta Daniels of the Trident Conversion Campaign, the sponsors of a mass demonstration in Groton, Connecticut two weekends ago at which 229 persons were arrested for trying to block shipyard entrances to guests arriving for the launch of a new nuclear submarine.

But it seems to be on the West Coast, with its high concentration of both defence-related industries and veterans of the anti-Vietnam campaigns, where the linkages are being most tightly drawn.

One focus in particular has been the relationship between the University



Flashback to the 1960s: anti-war protest fills the street.

of California and the two weapons laboratories which it manages for the Department of Energy. This link has long been a source of contention among university faculty and students and moves to sever it in recent years have been given a boost by a broader anti-militarism campaign.

Supporters of the current arrangement argue that being run by the university means the laboratories can both maintain the high quality of their scientific research, and remain free of industry or Washington-dominated influences to express their views. "The university connection is the best way to serve the people" says Ed Hammel of the Los Alamos laboratory.

Critics point out that every nuclear weapon in the US armoury was conceived, developed and tested by the two laboratories. "The laboratories are not academic institutions, they epitomise 'science with a purpose', says one long-time opponent, Professor Charles Schwarz of Berkeley's Department of Physics.

Ironically, those on both sides of the debate agree that, despite wide disparities in the technology, concern over the health hazards of nuclear power have linked the energy and weapons issues together in the public's mind.

Dr David S. Saxon, President of the University of California, sees public attitudes on both as a source of concern—but a situation for which scientists must share part of the blame. "The present unreasoning fear within this country and abroad of anything associated with the word nuclear is a reflection of an almost inexcusable failure within the scientific and pro-



Now nuclear power is seen as the guilty party.

fessional community involved in nuclear energy", he said recently.

"There has been a consistent unwillingness to react in responsible ways to the questions that members of the public ask. In too many instances the official attitude has been overbearing, arrogant and intolerant."

Dr Schwarz, on the other hand, feels that the type of concerns raised by the Harrisburg incident may—legitimately—spill over to what he considers a far greater health issue, namely the spread of nuclear weapons. "We have to show that the same institutions that run the nuclear power programme also run the nuclear weapons programme—and that we have been told the same lies. I am not against nuclear power in itself, but I am opposed to it because, as with nuclear weapons, I don't trust the people in control of it at the present time".

The university has itself been reconsidering its relationship to the two laboratories. A committee established in 1977 under the chairmanship of Dr William Gerberding, Chancellor of the University of Illinois, issued a report last year, suggesting that the university should continue to manage the laboratories, but through the operation of a powerful board appointed by the university, which would play a much closer role in overseeing the operation of the two laboratories than under present arrangements.

In an attempt to counteract charges that even under a board such as that proposed by the Gerberding committee, there would be little public discussion of the laboratories' activities, one university vice-president, Dr William Fretter, has proposed as an alternative arrangement the establishment of an advisory council to the university president, containing scientists, faculty members and students.

"I did not find the Gerberding proposals realistic, since the programmes of the laboratories—especially the weapons laboratories—are determined in Washington by the federal government, and it seemed unrealistic that these could be influenced substantially by a university committee", Dr Fretter said last week.

He argues that although the committee which he has proposed would only be an advisory one, it should

operate in public "since both the university community and the general community need more information on what goes on in the laboratories". Critics such as Dr Schwarz, however, maintain that since the committee would not deal with the laboratories' classified activities, and since it would have no executive responsibility—which would remain in the hands of President Saxon—it would lack any real teeth, and hence be little improvement on the current situation.

Debate within the university on the future relationship to the laboratories has been put temporarily on ice following the announcement in December that the Department of Energy was itself planning a review of the current arrangements. The department's report is due to be presented to Energy Secretary James Schlesinger next month, and is awaited with interest (particularly since, although being prepared by a subcommittee, the report is officially to be submitted by DOE's Energy Research Advisory Board—and this contains a number of individuals from the public interest community as specialists in alternative energy sources).

But if there is a pause in the official debate, grass-roots opposition is continuing to grow. The future of the weapons laboratories was among the issues raised at a mass rally held in San Francisco two weeks ago to protest at the opening of the Diablo Canyon nuclear power plant in the state, a meeting held under the shadow of the Harrisburg incident. And organisers of next month's demonstration at Livermore predict many thousands will turn up for a mass march, rally and 'peace conversion fair', with groups fasting at the laboratory gates, and others walking to the laboratory from all over California.

To judge from reactions elsewhere such activities are unlikely to be warmly welcomed by the university authorities. Last week a film crew was thrown out of Harvard University while trying to make a film about the 1960s protest movement. The film's director, Mr Jim Zinneman, admitted that a three-story mural showing some American soldiers trampling on Vietnamese "upset some faculty members and alumni". Nostalgia is not what is used to be. □

ISABELLE team denies setback

RUMOURS that the US ISABELLE project is having difficulties producing superconducting magnets for its 400 GeV proton-proton storage rings were denied last week by Dr Jim Sanford, the project head. In an interview with *Nature*, he said there were no problems with quadrupole magnet production, although they had run into difficulties with the dipole magnets.

Overall, progress was "90% satisfactory". "We are having problems in meeting the ultimate field of 5 teslas. We have reached 5 teslas in a model but not in the production prototypes. They are operating now at around 4½ teslas," he said.

The dipole magnets were first designed to operate at 4 teslas. The team made 13 model magnets and most of these exceeded this field. Recently the design was modified to operate at 5 teslas, and one model reached 5.1 teslas. However, when this was put into production, the magnets only achieved a field of 4–4½ teslas, Dr Sanford said. "We are not entirely sure what is causing this problem. Maybe it is the materials in the superconducting braid. We wanted to have a bigger margin than 5.1 teslas and so we added more niobium-titanium in the production, and in the process we may have lost some of the stability of the materials."

Production of the superconducting magnets is the major technological challenge of the ISABELLE project. The project has already had one setback—the US Department of Energy will only fund ISABELLE over seven years and not the five years the scientists had hoped for. However, Dr Sanford is confident the magnet problem will be solved by the summer so the contract for production can be issued by the end of the year. This will keep ISABELLE on schedule, and may even provide an argument for advancing to a 5-year target, said Dr Sanford.

In Europe, ISABELLE's competition in the race to produce the heavy intermediate vector boson, the CERN proton-antiproton experiment, is expected to produce hard evidence by 1982, said a CERN spokesman. □

UK and Sweden attack lead poisoning studies

A NEW US report on lead pollution published in *The New England Journal of Medicine* by a team of researchers from Harvard Medical School and the Children's Hospital in Boston has not been openly welcomed in Britain.

The study indicates that currently accepted lead levels may be set far too high to be safe for children in urban

areas. The team, headed by Dr Herbert Needleman, examined lead levels in children's milk teeth, which is considered to be a better indicator of long term exposure than blood lead levels.

Starting with a sample of 3,329 children, two samples matched for social and environmental variables including social class, mother's age and

parental IQ were constructed. The 58 high lead children (20ppm in dentine) and the 100 low lead children (less than 10ppm) were given standard psychological and mental tests. (The mean blood lead levels in the two groups were 355 µg/l and 238 µg/l, both of which are well within the normal range for children in UK urban areas.)

The results showed that the high lead children performed less well on all the tests including reaction time, word processing and standard IQ tests.

Professor Pat Lawther of St Bartholomews Medical School in London and chairman of a Department of Health and Social Security working party on lead pollution in the UK calls the Needleman study "the result of very careful work" but says that the statistics "have to be gone into in great detail" before he could evaluate it. "There are 39 variables subject to regression analysis, and besides, behavioural studies are very difficult" said Professor Lawther.

According to Anthony Tucker, science correspondent of *The Guardian* newspaper, the DHSS working party has been primarily concerned with criticising earlier studies that showed lead induced behavioural changes in children in the UK. "But since no studies of this standard or scale have been carried out in Britain or elsewhere it is difficult to see how its findings can be refuted" writes Tucker.

Meanwhile one of Britain's specialists

on lead whose work is supported by Needleman's study, Professor Derek Bryce-Smith of the University of Reading, was subjected to some extremely unprofessional behaviour when he visited Stockholm recently to take part in a panel debate on lead and children. His visit followed a minor furore caused by the publication (in the journal *Ambio*) of an article which he co-authored, alleging that body lead levels considered normal in children actually appear to be pathogenic.

The article had prompted denials from two Swedish researchers, one of whom—Professor Åke Swensson—agreed to take part in the debate. In deference to Bryce-Smith, the Royal Academy of Sciences, which arranged the debate, announced that it should be held in English. This was duly printed on the programme and all the Swedes complied—except one. Docent Carl-Johan Göthe, ignoring the chairman's admonition and in spite of the fact that there was no official interpretation provided, announced that he would speak Swedish. He then proceeded to attack Professor Bryce-Smith, coming to the

very edge of personal insult. A little later he answered a question in English.

But Bryce-Smith himself was more disturbed by the behaviour of Professor Magnus Piscator, the other critic of the *Ambio* article. Piscator published his critique in a Swedish-language medical journal, accusing Bryce-Smith—among other things—of distorting information in some of his reference material. He made no attempt to contact Bryce-Smith to make his charges in English, and even refused to participate in the panel debate, saying it was stacked with people sharing Bryce-Smith's views—which was not the case.

"The allegation of distortion is untrue and libellous as far as we are concerned", says Bryce-Smith. "Piscator's article was extremely discourteous and unprofessional. His behaviour is very irresponsible and not in the best traditions of science."

Professor Bryce-Smith was not impressed, either, with the level of the debate. "These people do not seem to be aware of recent literature on the subject", he said, citing the Needleman paper. □

Soviet science boss refused Academy membership

SERGEI P. Trapeznikov, the Soviet top Party boss for science, has been refused full membership of the Soviet Academy of Sciences. So far as is known, this is the first time that the academy has ever refused an application from a member of the Central Committee of the Communist Party of the Soviet Union.

Trapeznikov is chairman of the Science Commission of the Supreme Soviet, and as such, formally has both the State Committee for Science and Technology and the Academy of Sciences under his jurisdiction. His appointment, however, was made on political grounds, not scientific. He has the reputation of a hardliner, and during the 1960s vigorously opposed the economic reforms proposed by Professor E. G. Liberman, which were aimed at loosening the Party's hold over the economy.

Since his appointment as Chairman of the Science Commission in 1968, Trapeznikov has tried several times to get elected to the academy. In 1976, he finally achieved the rank of "Corresponding Member" (i.e. Associate Member). Election as Corresponding Member, however, does not require a vote from the full General Assembly of the Academy, but only confirmation by the general assembly of a decision already made by the relevant section.

Applications for full membership, however, must be discussed by the general assembly, and are then decided

by secret ballot—the academy is the last remaining body in the Soviet Union to exercise this method of voting. It is due to this right of secret ballot that Academician Andrei D. Sakharov remains a member of the academy, in spite of several attempts to have him ejected.

Sakharov, indeed, took part in the debate on Trapeznikov's candidacy, stating that the latter's works on the collectivisation of agriculture were not of sufficient scientific value to qualify him for admission. Trapeznikov was rejected by a majority of 212 to 137.

Regarding these figures, it is interesting that Mark Popovskii, a journalist who emigrated from the Soviet Union in 1977 claimed in his book *Controlled Science*, that secret ballot notwithstanding, there are certain members of the academy who would never dare vote against the election of the chairman of the Science Commission. Discussing just such an election as an example of the degree of "humility" the academy shows towards the Party, Popovskii states that the Chairman of the Science Commission (i.e. Trapeznikov) has within his competence the appointment of the directors of scientific institutes, "one of the most longed-for jobs in the country". Secret ballot notwithstanding, Popovskii suggests that in such an election, although the "rank and file" academicians can "play their game of democracy", those who hold the post of director of an

institute simply would not dare.

Popovskii also relates a number of other cases when persons of political status but insufficient scientific quality have been turned down by the academy. These include the present Minister of Education, V. P. Elyutin, and the Minister of Health B. V. Petrovskii. (The latter has in fact good medical qualifications, but medical personnel, however distinguished are not admitted to the Academy of Sciences—they must apply to the less prestigious Academy of Medical Sciences).

Some years back, however, the Academy of Sciences seems to have been more complaisant—during his term as Minister of Geology, Aleksandr V. Fedorenko managed to become a Corresponding Member (1953) and then a full Member (1966).

Why though should Trapeznikov and other politicians whose work verges on science be so keen for election to the academy? Is it simply a desire for increased status? Possibly. However, membership of the academy brings more than status; it includes a generous salary, and a number of valuable fringe benefits in housing and the like. Moreover, these are held, effectively, for life. Expulsion from the academy is virtually impossible, although it is reported that during the last few months the academy's statutes have been amended to ensure that anyone deprived of his Soviet citizenship would be automatically expelled.

Vera Rich

Czechoslovakia strengthens science and technology

LAST year, Czechoslovakia embarked on what was described as a "complex experiment in effectiveness and quality control"—which to Western observers seemed virtually a reform of the economy save that "economic reform", to the Czechs, is an expression tainted by memories of the Dubcek regime. Last month, the meeting of the Czechoslovak Federal Assembly carried the tendency further, by virtually rejecting the figures for the next Five Year Plan—an event unprecedented in the history of the Czechoslovak Socialist Republic.

One change associated with the "complex experiment" was the reorganisation of the pay structure for scientific and tutorial staff at universities and other higher educational institutions. Addressing the Federal Assembly last month, Prime Minister Lubomir Strougal observed: "The salary conditions of scientific and tutorial staff of the higher educational institutes [polytechnics and universities] were regulated with effect from 1 October, 1978. We believe this, however, to be only one partial step designed to raise the interest of specialists from scientific and research institutes [which do no teaching] and from practical places of work in taking up jobs in higher educational institutes."

Although details of the new "con-

ditions" are not forthcoming, the trend accords with the general tenor of Strougal's speech and the other discussions in the General Assembly.

Czechoslovakia is the most reluctant member of the Comecon bloc when it comes to the purchase of foreign technology or know-how; the economic proposals outlined last month envisaged a cut-back in imports of all kinds and a greater dependence on home resources.

Officially, this change was linked to the word energy situation. Since September, 1976, when the Soviet Union suddenly increased oil prices to Comecon, Czechoslovakia has had a growing energy problem, which has been only partially met by the staggering of working hours. Strougal's speech contained six major proposals in the energy sector: expansion of capital expenditure on home fuel and energy production, a crash programme for the development of the North Bohemian lignite reserves, intensified research into the "complex of problems" ranging from investment to social welfare) associated with plan fulfilment in the deep mines of the Ostrava-Karvina area, an extension of nuclear generating capacity to 3,500 MW by 1978 and 8,000-10,000 MW by 1990, further participation in transit programmes, allowing "various forms

of energy" (eg, natural gas) from the Soviet Union to cross Czechoslovak territory and the implementation of fuel-saving programmes, aimed at saving some 20m tonnes of fuel per year.

Regarding this energy programme, Strougal noted that the total savings envisaged would not be possible immediately, but that substantial progress "must be registered in the remaining years of the current Five Year Plan, and especially in the next Five Year Plan". In his main speech the Prime Minister did not, of course, make any reference to the accidents which the Charter 77 movement allege took place at the Jaslovské Bohunice nuclear power station in January 1976 and February 1977.

It was left to a relatively minor member of the Assembly, Deputy Dana Kancirova, to raise this inauspicious subject. Even she approached it in a roundabout manner, asking for an explanation concerning the current Austrian press campaign about the safety of nuclear power stations. Mr Strougal answered, somewhat airily, that "our present and planned nuclear power stations are of the Voronezh type, different from the one at Zwentendorf". The alleged fatal accidents at Jaslovské Bohunice, he added, were simply "a fabrication of bourgeois propaganda". **Vera Rich**

Islamic scientists prepare for UNCSTD

Ziauddin Sardar discusses the Muslim countries' views on development and the role of Islamic science

THE Islamic Secretariat is to submit a position paper, representing the views of its 42 member countries to the United Nations Conference on Science and Technology for Development in Vienna next August. The paper is the final outcome of a conference held in Jeddah on 17-21 March and has at least two novel features: it is the first effort by the Islamic bloc to represent an Islamic viewpoint on science and technology at the level of the United Nations and it forces the Muslim countries to recognise that there can be no effective development without the evolution of indigenous science and technology.

Implicit in the first point is the assumption that there is an Islamic alternative to the conventional practice of science and technology. That the Jeddah conference could not go beyond vague statements of this alternative is not surprising: the Muslim civilisation has been dormant for over three hundred years and current ideas on Islamic

science and Muslim technology emerged only at the turn of the decade. Clearly there is a great deal of work and much analysis to be done before anything concrete emerges. The Islamic Secretariat paper provides recognition to these ideas and should give them an international hearing.

The second feature is important because, when the paper is endorsed by the Tenth Islamic Conference of Foreign Ministers in May, the Muslim countries will become actively committed to the establishment of ministries and/or other high-powered bodies for science and technology. This may not appear to be much of an achievement from the perspective of the industrialised countries, but only half a dozen of the 45-odd Muslim countries currently have ministries and other national bodies devoted entirely to science and technology.

Billed as "The First Muslim Science Conference", the Jeddah meeting was convened by the Ninth Islamic Confer-

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الإسلامية العامة لمنظمة المؤتمر الإسلامي

Emblem of the Islamic secretariat

ence of Foreign Ministers, held in April 1978. The science conference itself was a shambles. Of the thirty-odd delegates who attended only seven could be classified as scientists; the rest were all career diplomats. Although it was never openly admitted, the dominant presence of the civil servants was clearly embarrassing to the scientists who were eager to produce a powerful position paper.

What is surprising is that the scientists managed to carry the conference and produce a coherent and

reasonably well argued paper. They see UNCSTD as the first step towards the establishment of a "new world order in science and technology". Dr A Abou El-Azm, who is tipped to be the first director of IFSTD, argued for a strong action-orientated paper that does not undermine the position of the Group of 77, and Dr Ali Mohammed Kamel, a consultant to the Arab League Educational, Cultural and Scientific Organisation (ALESCO) repeatedly asked for the paper to be connected with the call for a New International Economic Order.

Dr Waqar Husaini of the Civil Engineering Department, King Abdul Aziz University, was more concerned with emphasising the issues of ethics and morality of science. "Islamic development", he argued, "is concerned with individual and self-purification and with growth that does not transcend the ethical boundaries of Islam. Science and technology do not have an independent existence under Islam. To the contrary, they are subject to the value principles of Islam"—a point that was also echoed by other delegates.

Dr Yalgin Tuncer of Middle East Technical University was not very optimistic about the outcome of UNCSTD and argued that the Islamic position paper should be addressed not so much to UNCSTD but more to Muslim countries. "We should have a crystallised model of Islamic science and technology and its role in development; and we should offer this model to Muslim countries for study and application", he said. It was finally agreed that the paper will address the UNCSTD meeting, the Muslim countries and IFSTD.

The paper airs many concerns common to the developing countries; the lack of awareness in the Muslim world of the key role of science and technology in development; the quality and quantity of available manpower; the brain drain; the exploitative practices of western governments and multinational corporations in the field of technology transfer; lack of information on the choice of available technology; and the adverse repercussion of the politics of aid.

Unfortunately, examination of these issues is devoid of self-analysis. Placing the shortcomings squarely at the door of the West has become a common practice with the developing countries. The Islamic Secretariat's paper could have provided a lead by closely examining the attitudes and outlooks that prevent science and technology from taking indigenous roots in the Muslim world.

Also absent from the paper is an awareness of the ideological stance of science. The Islamic Secretariat's paper asserts that "there are no ideological obstacles to a vigorous introduction of science and technology in Muslim coun-

tries". This is not altogether true. Traditional Muslim intellectuals do not see science as an entirely value-free, apolitical activity; and their experiences have confirmed their views. The Islamic Secretariat's paper largely overlooks this viewpoint and asserts that problems only exist in the realm of transfer and adoption of technology.

However, a slight awareness that the situation may be more complex appears in the statement that "it is not always possible to separate science and technology from the philosophical background and social forms attached to them in their country of origin". Hence, it is argued, it is necessary to develop an Islamic philosophy of science. The paper states: "Science is a common human heritage and almost all nations have contributed to it at one time or another. Muslims, in particular,



have made some of the most decisive contributions. . . . Hence it is an absolute fallacy to see science and technology as the sole product of Western culture". But there is an inductive leap that leads the paper to conclude that it is therefore possible to fit conventional practices of science and technology into Islamic social and ideological systems. The first step towards this goal is said to be the popularisation of education, training and the professional practice of science and technology. Here there is an acute shortage of good technical translators and qualified scientists who can teach in indigenous languages. Those who can teach do so only in a foreign language, for they themselves were either trained abroad, or by foreigners locally. Scientists and technologists trained abroad, particularly, present a tremendous resistance against popularisation.

The paper rightly blames the frustration of local scientists on the *en masse* transfer and purchase of western technology. This is why the Muslim countries "have not developed locally effective institutional mechanisms and expertise to ensure performance of various functions for assessment and

selection of appropriate technologies and for successful implementation and adoption of these technologies in the productive sectors". But in turn, this technological weakness is the main reason for the failure of technology transfer and for the technological dependence of the Muslim world. The prescription for shaking off this dependence asks Muslim governments to individually and collectively: formulate their policies for choice, transfer, and development of technology; build up an infrastructure for creating and using technology; and develop competent manpower.

Although it is not specifically stated, the paper assumes that at present Muslim governments do not have science and technology policies worthy of the name. A comprehensive science and technology policy is seen as a "fundamental pre-requisite for self-reliance and self-development". Further, this policy "should be integrated with the Islamic socio-economic objectives and policy and be consistent with its development priorities . . ."

The best way to turn the brain drain into the brain gain, says the paper, is to introduce and strengthen the internal "pull-factors". Such "pull-factors" could include "an Islamic socio-political environment, facilities for intellectual growth and professional satisfaction, logistic support at home and place of work that enables the scientists and technologists to be efficient and productive, proper salaries and privileges, merit-based promotion and recognition through a system of rewards, in-service training, continuing professional advancement, visits to advanced countries, etc."

This oft-preached solution has one unusual recommendation: the developed countries should be persuaded to adopt legal measures against immigration and employment of skilled Muslims from developing countries without their governments' consent.

Science and technology resources in the Muslim world are scarce. The paper's plea to the Muslim countries to share and pool their resources, therefore, makes a great deal of sense. Many Muslim countries face similar development problems. Obstacles to development in these areas could be eliminated by effective cooperation and joint action programmes. IFSTD, the paper states, will be a catalyst in this process of cooperation and coordination.

Despite its many shortcomings the importance of the Islamic Secretariat's paper for the Muslim world cannot be underestimated. Even if only half of its recommendations are actually followed up by the Muslim countries, it could change the status of science and technology in the Muslim world. And that would be no small achievement. □

news in brief

Gargamelle may be scrapped: CERN's heavy liquid bubble chamber, Gargamelle, which was the first to detect the weak neutral current and has been in operation since 1970, may be at the end of its life. Last year a leak was detected in the chamber that proved to be easily identifiable and repairable. But the chamber was sent to the factory for further inspection, to check the welded joints, and micro-cracks were discovered in the welds. The cracks are currently under investigation and a decision will be taken on the chamber's future at a meeting on 19 April. Engineers have given negative advice saying that repairs will be very costly, of the same order of magnitude as the cost of building a new chamber. Another consideration is whether the chamber would be in violation of Swiss safety standards. Gargamelle is used as a neutrino detector and its loss would leave only the BEBC heavy liquid chamber for neutrino physics, a considerable cut in detecting power. The loss would come at a particularly inopportune moment, as CERN is to reach 450 GeV this summer, doubling the neutrino flux to the two chambers.

Soviets respond to Harrisburg: Soviet nuclear planners have taken the opportunity of the Harrisburg disaster to defend their own commitment to fast breeders. Within the last few days, Moscow radio has put out two major interviews which, while not mentioning Harrisburg explicitly, are a clear comment on the situation.

In the first, an English-language transmission to North America, Dr Andronik Petrosyants, the Chairman of the USSR State Committee for the Utilization of Atomic Energy, said that although to date the Soviet energy programme had been based mainly on 'conventional reactors' (with experimental fast-breeders at Obninsk, Dmitrovgrad and Shevchenko), long-term plans envisage a change-over to fast-breeders, a field in which Soviet scientists "cooperate with their counterparts in the US". Petrosyants added "Only such reactors will enable the industry to develop sufficiently fast and on a large enough scale". Later he explained that the Soviet applications of fast-breeders, which "are limited by scientifically motivated standards, present no radiation hazards".

In a programme for the home audience, Anatolii Aleksandrov, President of the Academy of Sciences of the USSR described Soviet plans for constructing nuclear power stations in urban residential areas, which should, he claimed, halve the cost of district heating. Plans are also under way, he said, for using power stations as a source of heat to cut the cost of "relatively expensive technological processes such as those involving powder metallurgy".

Orlov told to stop issuing research notes: Yuri Orlov, the Soviet physicist at present serving a 7-year labour-camp sentence for his activities in defence of human rights has been forbidden to include in his fortnightly letters home any mathematical formulae or other material which the camp guards cannot understand. Ironically, his wife received this information about 10 days before *Nature* published extracts from his letters, in which he described his attempts to keep up some form of theoretical research.

Banning of the intellectual activity of dissidents is nothing new in Russia. In 1847, the Ukrainian poet, Shevchenko, was sentenced to 25 years in an army penal battalion, "with the express prohibition of writing or painting", added to his sentence in the Tsar's own handwriting. It is not known at what level the ban on Orlov's intellectual activity originated. Mrs Orlova thinks that it probably originated with the camp guards themselves. However, a friend of the Orlovs told *Nature*, no guard would take any initiative

he did not think would be approved higher up. This friend also pointed out that in Orlov's last "scientific" letter from the camp—a paper on wave probability—he indicated by a periphrasis that he hoped it would be published abroad.

Portugal doubtful about Soviet Atlantis find: Recent claims by Soviet oceanographers that they have discovered traces of a city on the floor of the Atlantic have been treated somewhat sceptically by their Portuguese opposite numbers. After discussing the "finds" with the Soviet team, Dr Marcello Vasconcelos, head of the Portuguese National Institute for Fishing Research, admitted only that "It is undeniable that they have found something". He and his colleagues at the Institute could not give a professional opinion on the reported find, he explained.

Dr Vasconcelos said that the Soviet scientists appeared to be "highly optimistic" about their photographs which, they claim, show ruins of a city some "320-480 km" off the coast of Portugal, in the direction of its "mid-Atlantic island possession, Madeira". Dr Aleksei Aksenov, the head of the Soviet team, claims to have taken eight photographs, showing "vestiges of walls and stairways". Further details, including the depth of the alleged finds, will, according to Dr Aksenov, be announced after further study of the photographs in Moscow. Soviet opinion, he explained, was that the discovered remains could well be the "lost continent of Atlantis".

Soviet oceanographers would appear to be having great success recently in explaining Atlantic "mythology". Last year, another oceanographic expedition reported huge "vortices" in the Bermuda triangle region.

UK proposes major microprocessor research and training programme: The Science Research Council in the UK has adopted the recommendations of a Council panel which call for a major programme of additional academic research to "help the UK get maximum benefit" from microprocessors and programmable electronic technology. The panel makes specific recommendations in the areas of education and training, new computer applications and new computer technology. In education, the panel proposes a centrally coordinated programme of six five-year projects to expand existing commitments such as the National Development Programme in Computer Assisted Instruction. The panel envisages 1,000-2,000 "work stations" that will use the new technology for education and it calls for the appointment of a Programme Director "at an early stage". In addition the panel proposes 50 research studentships per year in computers and microelectronics, conversion courses for "arts graduates (or unemployed teachers)" and additional fundings to attract PhD and MSc students.

In new computer applications the panel emphasises the importance of industrial robotics both for UK application and for export. The panel asks the SRC to appoint a Programme Director to carry out an "in depth study" of the UK situation over the next 12 to 18 months and it recommends the creation of an SRC professorship in this field "in a major location." The Rutherford Laboratory is proposed as a centre for research into increased uses of microprocessors in measurement and instrumentation as well as for research into the next generation of silicon chip design and test automation.

The SRC has appointed an Implementation Group chaired by Professor J. Brown of Imperial College to draw up detailed costs and to liaise with other concerned governmental bodies.

Steady progress on the 'long march' to modernisation

Jen Tsi Yang, professor of chemistry at the University of California, San Francisco, on the revitalisation of science in China

THE People's Republic of China is embarking on a grand programme of Four Modernisations: in agriculture, industry, national defence, and science and technology. An aphorism by the late Premier Chou-En-lai, "Dare to think, dare to say, dare to do! Work hard, work with energy, work with ingenuity!" can serve as a battle cry for what is being called a New Long March (*Xin Chang Zheng*) or even a New Liberation (*Xin Jie Fang*). After a turbulent decade from 1966 to 1976, an openness (within limits, of course) and a new mood of enthusiasm are evident. During a recent visit to China my hosts talked to me uninhibitedly about many subjects, both scientific and more wide-ranging. Amongst them were some horrific stories—for which the now toppled villains were blamed in nearly all my conversations—which are better left for future historians to sift through. My observations on science in China are not intended to be comprehensive, but will indicate the progress being achieved.

Education is the key to the modernisation programme. China is racing to train a vast phalanx of scientists and technologists. The country lost a generation of educated manpower during the Cultural Revolution, starting in 1966. Schools were closed for several years, and the students of universities, colleges and secondary schools went on a rampage while the teachers were subjected to repeated confrontations and inquisitions. Yet these students received promotion every year and "graduated" automatically. Millions of them were later sent into the countryside and still live there. The sudden change in political climate in October 1976 has produced a renaissance fervour for learning. The few cities I visited, including Shanghai, Nanking and Peking, reflect this new atmosphere now sweeping the country. Books on science, technology and primers of foreign languages, especially English and Japanese, are in great demand, and a new English-Chinese dictionary has already sold out. The libraries are once again crowded.

Nationwide college entrance examinations were held in December 1977 and July 1978. The applicants were appraised morally and physically as well as intellectually. No longer, I was assured, are the children and grandchildren of workers, peasants and soldiers automatically favoured for admission. To avoid corruption in the form of backdoor dealings, each appli-

cant was allowed to check his or her score, calculated to the first decimal, against the announced pass mark, which was adjusted geographically to give a balanced distribution of successful applicants. Having cleared this first hurdle, each applicant had a physical checkup and an evaluation of his or her moral character. Both former 'graduates' from the bad years and those fresh from high school competed for this educational opportunity. Many did well in the exams by dint of cramming, either alone, or with the aid of tutors.

The present education system comprises periods of five, three and two years at elementary, junior high and high schools respectively, and four years in college or university (five years in medical college). Currently, 88 institutions are designated as *chong dian* (literally, main-point) or key universities. Initially, about 200,000 freshmen were to be accepted in 1978, but this number has been enlarged, perhaps even doubled, and many universities have set up branches to accommodate the increased enrolment. In addition, the graduate training programme has been restored as a three to four year course, although details are still to be worked out. This has led to the danger that the teaching staff could be overburdened by the combination of increased teaching loads with new activity in research. More serious is the risk that tensions may build up between the educational "haves" and "have-nots", especially those millions sent to the countryside, who do not get as far as the entrance exams.

In the 1950s China adopted the USSR educational model, which is now being modified. At present a comprehensive university is essentially a large college covering both letters and science, while schools of engineering, agriculture and medicine are separate colleges or universities (depending on size). Under the old system, incoming freshmen were required to choose a specialised subject (*chuan ye*), and the students were denied a spectrum of courses beyond their specialities. China's new plan is to teach basic courses for 2½ to 3 years and the students will have freedom to choose one *chuan ye* in their final year.

Three major speeches delivered at the National Science Conference in March 1978 have now been published in the "Documents of the National Science Conference" by the People's

Publishing House (*Renmin Chubanshe*). They contain the blueprint for the Four Modernisations. The State Science and Technology Commission, headed by Vice Premier Fang Yi, now administers all the research programmes in the Academia Sinica, universities and colleges under the Ministry of Education, and various industrial ministries.

The Academia Sinica (or the Chinese Academy of Sciences) is traditionally the cornerstone of basic research in the natural sciences. The academy has many branches all over the country and it also administers four universities. (In addition, there are municipal and provincial academies of sciences.) At present the academy has more than 100 research institutes in some 20 cities, Peking having 40 and Shanghai 15. There are about 30,000 researchers and 20,000 administrative and non-technical staff. Research institutes also train their own graduate students. It seems to me that these institutes could benefit from bringing in researchers trained elsewhere, and from having their scientists participate in university and college graduate training. Such cooperation between the institutes and schools is crucial to the crash programme of modernisation. While a certain degree of competition between institutions is an incentive for excellence, Chinese researchers face a real problem in "mountain-topism" (the establishment of rival empires); because of the shortage of scientists, both the universities and research institutes want to keep their best trained graduates. I believe that this is a waste of manpower, and furthermore, the in-breeding does not expose the graduates to a suitably broad spectrum of knowledge. Ideally, the universities should train the graduates and the institutes train the post-doctoral staff (although no degrees are offered in China).

Gone are the anti-intellectual Workers' Propaganda Teams which once controlled the institutions, and established scholars have again been called upon to administer institutions, albeit under party leadership. While the loss of a generation of educated young is most tragic, one should also spare a thought for the frustrated middle-aged researchers who have wasted the most creative decade of their lives. At present China's institutions have many senior faculty and researchers, but not enough well-trained junior investigators under the age of 35. This gap will close when a new crop of graduates joins the rank of their elders, for junior faculty and staff are again being professionally evaluated for pro-



Education is the key to modernisation

motion, after a lapse of more than ten years. They will succeed the ageing generation of Western-trained scholars and will have to shoulder the main burden in the immediate future. I can attest to the fact that the new political climate has brought about a euphoria amongst Chinese educators and researchers, both young and old.

Under the incentive to catch up rapidly, "glamorous" research projects are naturally the most attractive, and I think China must be very careful that fundamental research does not suffer as a result. Genetic engineering is a case in point, for despite considerable enthusiasm for such topical research, the universities and research institutes are really so poorly equipped at present that I think it unwise to seek glory and neglect the basic facilities.

Visiting scientists are welcomed as foreign guests (*waibin*) and given VIP treatment. Such visits expose Chinese researchers to the current state of knowledge and level of thinking in their fields. China-born scientists now living abroad, often called the people's relatives, are especially sought after, for their ability to teach with no language barrier and to advise with the benefit of a common cultural background. Many of us, with close kinfolk in China, have made repeated visits in recent years, for while we are loyal to our adopted countries, we are proud of our heritage and most of us are willing to contribute regardless of ideological differences. Normalisation of Sino-American relations is bound to multiply such scientific exchanges. Not many such visitors can extend their stay for too long without affecting their own research but sabbatical leaves and collaborative research projects may provide longer-term scientific contact. China is now sending abroad hundreds of graduate students for training, experienced researchers to expand their knowledge and numerous scholars to attend international meetings. The impact of these returned scientists and technologists is bound to be immense and not confined to science.

Chinese scientific journals are being revitalised. The bimonthly *Scientia Sinica*, a comprehensive journal for the natural sciences, with some articles on agriculture, medicine and technology, resumed publication in 1973 and is scheduled to be published monthly in 1979. Most, but not all, papers in the Chinese and foreign (predominantly English) editions are identical. Currently, the editor-in-chief is a vice president of the Academia Sinica; he is assisted by an associate editor and an editorial committee of 106 members as well as an editorial staff. Other Chinese journals such as *Acta Biochimica et Biophysica Sinica* have both Chinese and English abstracts. In a departure from the formats of early years, political slogans and quotations are generally absent from scientific texts, and collective (anonymous) authorship by a laboratory may also be declining. *Kexue Tongbao* (*Science Bulletin*), which was also re-launched in 1973, will concentrate on short communications in sciences in 1979. This monthly publication will soon become semi-monthly, and a foreign edition is being planned. Recently, *Nature* has accepted the first paper from the People's Republic of China (Ho, Y.S. & Tsou, C. L. *Nature* 227, 245-246 (1979)). This could presage a trend for Chinese scientists to summarise their best work in foreign journals. English has now become the language of science, and Chinese students once again study English from the third grade through the college freshman year.

The term 'science management' is frequently heard in China these days. The best use of available manpower and resources, and the financing of the astronomical cost involved, are central to the success of modernisation. In October 1978 Vice Premier Fang Yi toured Western Europe, and Yu Wen, secretary general of the Academia Sinica, headed a delegation to study US science policy-making, peer review, and research and development management. Similar delegations of science managers are also being sent abroad.

But mobilisation of bureaucrats in any country is not easy. In Peking a street sign for pedestrians reads: "one, slow; two, look; three, cross the road," and this rubric has been applied to those cadres who, uncertain in which direction to proceed, hesitate and prefer to cleave to established routines. The New Liberation should be a liberation of thought, for only then can "a hundred flowers blossom!" The unparalleled vicissitudes of the past decade have left many people with a sense of *xin you yu ji* (the heart still palpitates).

It is often said that Chinese scientists work at a slow pace. This I believe is no reflection on their energy and competence; they have simply been left with so appalling a legacy of problems that they need time to re-adjust. Shortage of technical assistance and lack of modern facilities must be remedied. One mundane fact is that Chinese intellectuals must spend much time on domestic tasks. Young people could easily spend one third of their working hours on non-scientific chores. It might take a woman one hour or so for the daily grocery-shopping (the majority do not have refrigerators). They wash clothes by hand. Couples with babies too young to go to the nurseries must cope with the baby-sitting problem. In addition, both husband and wife work; this further reduces their working hours on science. I believe that it would be detrimental to the national interest to treat the intellectuals as a superior class, which may become alienated from the masses, but workers would become more efficient if they were relieved of some of the more acute problems of daily life.

China can accomplish almost anything, but not all at once. There is always a danger of trying to do too much too fast when political and economic conditions may not yet be ripe to absorb such drastic changes. After nearly 30 years the people are demanding a modern nation with a higher standard of living, and over 80% of China's population live in rural areas (compared to under 4% in the US), where the struggle for the necessities of life is more arduous than in the cities. The scientists and high officials all want to speed up the modernisation programme, but the bureaucrats may be too slow to make the necessary response. China-watchers estimate that the programme will require several hundred billion dollars over the next eight years. With Chinese oil still in the ground, and little to export for raw materials, China's economic problems can be tremendous. But the Chinese people are pragmatic and determined, and given unity, stability and unanimity of grass-roots support, China should succeed in her long march towards modernisation. □

correspondence

Association of Geoscientists for International Development

SIR,—Your timely editorial "After geodynamics, what?" (15 February, page 503) was read with interest.

From the tone of the editorial, however, it appears that you have not yet become familiar with the Association of Geoscientists for International Development (AGID). Originally conceived at a symposium on the role of the geosciences in international development at the 1972 International Geological Congress in Montreal, AGID has grown to a membership of 1,100 geoscientists in 95 countries in its roughly five years of active existence. In this time it has held several symposia and workshops aimed at fostering technology on problems in developing countries, and, more particularly, at increasing the capabilities of developing country geoscience communities. Such topics as geoscience education in developing countries (Australia, 1976), geochemical exploration in the tropics (Zambia, 1977), and mineral exploration in the tropical rain forest (Venezuela, 1977) have been treated in this manner.

Among AGID's several publications are a quarterly newsletter, a directory of university geoscience departments in developing countries, a bibliography of groundwater reports pertaining to LDC's, and a critique of geoscience-related development aid.

Though it has kept a low profile in many 'developed' nations, AGID is well known in its area of emphasis from the abovementioned workshops and publications, for its surplus literature exchange (enabling organisations with insufficient foreign exchange for purchasing geological publications to obtain such materials that were donated as surplus by others), its appropriate technology referral and other services, and by the activities of its members.

AGID has sometimes been considered mainly as a means of technology transfer. But technology transfer is not AGID's only purpose, nor, certainly, is this an activity unique to AGID. Perhaps its unique challenge is to overcome the lack of emphasis on, and knowledge of, the peculiar geological environments found in developing countries which by themselves currently have limited resources for attacking these problems individually. Basic problems such as the effects of tropical weathering on geochemical dispersion, and of seasonally fluctuating water tables and surface wetness on geophysical exploration in tropical environments have received almost no attention; and engineers are often still caught designing structures around the assumption that a granite will hold a steep slope indefinitely (when the feldspars quickly weather to clay in the humid tropical environment, producing rapid slope failure). For the above reasons the need for an international institute, somewhat similar to the International Centre for Theoretical

Physics at Trieste but located in a tropical environment, is even more critical to the geosciences than to theoretical physics. Although AGID's workshops have attacked some of these problems, the need for a continuous institution directed at improving geoscience capabilities worldwide has been a goal of the Association since its inception. It has just completed an overall plan for such an institute, based on the experiences gained from its workshops and of its members.

The Association has received generous support from the Canadian International Development Agency, the (Canadian) International Development Research Centre, and the governments of Venezuela and Nigeria. Modest contributions have come from other sources, such as the Commonwealth Foundation. Nevertheless, AGID's accomplishments have been achieved on a shoestring budget.

From this you can see that the "secretariat" that you are seeking already exists. It has an advantage over attempts to organise such an effort from other existing institutions in that it is already in existence solely to develop the geoscience community where it most needs development. With its broad international base and its headquarters in Caracas it is less likely to become misdirected in its efforts than might a newly created secretariat in Europe or North America.

AGID heartily welcomes partners in its activities. People interested in its goals, as well as financial support are solicited. It is also interested in assisting in ongoing or planned projects, should such assistance be desired, and consistent with its goals. Correspondence can be addressed to Dr A. Bellizzia, Secretary, Association of Geoscientists for International Development, Ministerio de Minas and Hidrocarburos, Torre Norte Piso 19, Centro Simon Bolivar, Caracas, Venezuela.

Yours faithfully,

DAVID HASTINGS

*Department of Geology and
Geological Engineering,
Michigan Technological University,
Michigan, USA.*

Nigeria needs scientific leaders

SIR,—I was interested in Lynette Hamblin's report of Professor Ekong's speech at a recent UNESCO symposium (18 January, page 168), and particularly that she considers lack of scientific leadership to be the principal reason for the low scientific output.

At the time when I left the University of Ibadan, I felt that the leadership of that university, in organic chemistry at least, was in good hands with Professor Ekong; but within a very short while he himself had left to take up university administration.

Professor Ekong is not the only leading chemist in Nigeria to have left university teaching and research for administration, in some cases at least quite unwillingly. In Nigeria there are a number of able administrators of one kind and another, whereas there are very few capable scientific leaders, and I question whether the move of scientists into administration is really beneficial, whatever may be the case in more developed countries.

Yours faithfully,

D. A. H. TAYLOR

*Department of Chemistry,
University of Natal.*

Soviet reactor safety

SIR,—In your report on Soviet energy (25 January, page 258) Vera Rich reports on the "accident" in BN350, the Russian fast reactor on the Caspian sea. By the use of her words "it is presented as" she seeks to imply that the "accident" was not in the steam generators and that some accident occurred in the reactor core itself. In fact, the full details of this "accident" have been known for many years in the West and have been fully reported in international conferences, for example at the 1978 Bologna Conference (D. S. Yurchenko, *et al.*, *Operating Experience with the BN 350 Fast Reactor (1972-77)*; IAEA Symposium on the Design, Construction and Operating Experience with LMFBRs, Bologna, 10-14 April 1978), and many designers have visited BN350 subsequent to the "accident".

The presentation adopted in the article in *Nature* seems likely to mislead and to cast unwarranted doubt both on the integrity of the Soviet physicists concerned, and on the safety of the fast reactor as a power generator.

Yours faithfully,

R. D. SMITH

UKAEA, Risley, Cheshire, UK

Intuitive energy figures

SIR,—P. T. Landsberg (5 April, page 502) expresses the hope that his energy figures carry an intuitive meaning. As a basically illiterate mathematician, may I say that they do. They convey the impression that Mr Landsberg wishes to encourage the belief that natural sources of energy are entirely sufficient for our needs; and that he considers it prudent to publish figures setting out the possible power yield from deserts, without demonstrating the energy investment required to achieve it.

I will gladly sacrifice the assistance of 60W bulbs per capita even for 10¹¹ joules—in the service of comprehensive energy budgets on all energy projections illustrative or real, alternative or conventional.

Yours faithfully,

DAVID GREEN

Pembrokeshire, Wales

news and views

Nonradial and nonlinear stellar pulsation

from Douglas Gough

IN the past two decades the theory of the pulsation of the Classical Cepheid and RR Lyrae stars has reached a high degree of sophistication. This kind of pulsation is the simplest mode of oscillation a star can undergo: it is periodic and the motion is purely in the radial direction. Although there remain some niggling discrepancies between theory and observation the agreement is sufficient to convince most astrophysicists that our ideas are basically correct. Thus we seem to have a firm foundation from which to extend our studies to stars whose oscillations are nonradial and non-periodic. In recent years considerable attention has been devoted to such stars, and last month observers and theorists who work in this field attended a workshop* at which β Cephei stars, δ Scuti stars, ZZ Ceti stars and the Sun, were discussed.

Walter Fitch (Steward Observatory) reviewed observations of variable stars of δ Scuti and related types. These stars pulsate at low amplitude, and many exhibit two characteristic frequencies which bear a ratio close to that of two small integers. Consequently much of the subsequent discussion concerned direct resonances between two modes of oscillation. Arthur Cox (Los Alamos Scientific Laboratories) reported his failure to reproduce this behaviour theoretically from initial value integrations, even when the resonance conditions had been carefully engineered, and Robert Stellingwerf (Rutgers University), who had analysed the stability of pairs of singly periodic limit cycles of potential double mode Cepheid models, never found both cycles to be simultaneously unstable to linear perturbations. The double mode behaviour remains unexplained. During discussions of parametric resonances, it was pointed out that many of these stars seem to exhibit characteristics of strange attractors. Some δ Scuti stars appear to pulsate in many modes simultaneously;

Wojciech Dziembowski (Copernicus Astronomical Centre) estimated that nonlinearities developed by any one mode alone were too small to limit its amplitude to a value as low as those observed, and concluded that mode interactions must be responsible. Definitive calculations have not yet been performed, but techniques developed for studying oceanic gravity wave interactions and plasma turbulence are available for tackling problems of this kind. We can therefore anticipate considerable advances in this study in the near future.

A class of stars for which there is no convincing explanation is characterised by β Cephei. Myron Smith (University of Texas at Austin) reviewed the observations. The stars are of spectral type B, and lie in a strip in the Hertzsprung–Russell diagram a little above the Main Sequence. Mike Jerziewicz (Wrocław University Observatory) and C. Sterken (Free University of Brussels) reported new observations and pointed out that almost all stars in the β Cephei strip show signs of variability. They appear to pulsate in both radial and nonradial modes. As with the δ Scuti stars simple period ratios are found, which suggest again that resonance mechanisms are operating. Frequency splitting, presumably by rotation, has been measured, which offers the exciting prospect of trying to infer the angular velocity within these stars. Unfortunately we are not yet in a position to do this because the modes of oscillation have not been unambiguously identified; different workers expressed contradictory opinions about the modes they thought were responsible for the variability.

An intriguing property of some β Cephei stars is that they switch from one mode of oscillation to another on a timescale of no longer than about 10 periods. Smith argued that this is evidence that the oscillations are confined to a rather thin outer layer of the star, because otherwise it would be difficult to envisage how dissipative processes could effect the enormous energy transfer that would be involved. Others contradicted that claim, citing simple nonlinear oscillators that can alter their character on a dynamical

timescale. It is unlikely that it will be established in the near future whether such oscillators actually represent the behaviour of β Cephei stars in any way, because the basic physics of the variability is not yet understood.

How are the oscillations driven? Morris Aizenman (National Science Foundation) reviewed the many ingenious ideas that have been proposed in the past, all of which have failed. A recent suggestion by Stellingwerf that the mechanism is no more than the Eddington valve that drives classical Cepheids and RR Lyrae stars was debated. He proposed that interpolation in opacity tables on too coarse a grid had led to an underestimate of the efficacy of the valve, but Arthur Cox, one of the chief suppliers of opacity data to the astrophysical community, claimed that though finer resolution decreased the stability of the theoretical models it was never sufficient to render them unstable. The suggestion was made that if all the mechanisms reviewed by Aizenman were operating in unison the sum of their contributions might be sufficient to maintain the pulsations against dissipation. This idea, which is reminiscent of an early suggestion for solving the solar neutrino problem, was unenthusiastically received.

Solar oscillations

A significant fraction of the workshop was devoted to discussing oscillations of the Sun. First, Henry Hill (University of Arizona) reviewed the observations spanning the period range 3^{min} – 160^{min} and discussed the evidence already in the literature for the oscillations in the data being of solar origin. There followed a sequence of presentations of new observations and discussions of the longer period oscillations. Discussion concentrated mainly on two issues: the form of the oscillations in the upper atmosphere and the evidence for phase coherence.

By comparing different diameter measurements made at the Santa Catalina Laboratory for Experimental Relativity by Astrometry (SCLERA), Hill argued that the amplitudes of oscillation rise more steeply with height above the photosphere than can be

*The workshop 'Nonradial and nonlinear stellar pulsation' was organised by Professor Henry Hill and held at the University of Arizona on 12–16 March 1979. The proceedings of the workshop will be edited by Professor Hill and published in about 18 months' time by Springer Verlag in the series 'Lecture Notes in Physics'.

comfortably accommodated within the framework of linear theory. At first sight this should be no cause for alarm, because the amplitudes thus inferred in the low chromosphere are so great that nonlinearities must surely be important. Nonetheless several participants were uneasy with the result, because in the photospheric regions, where presumably linear theory is valid, the eigenfunctions have the appearance of waves penetrating an evanescent region from above yet having frequencies characteristic of the resonating cavity beneath. Tuck Stebbins (Sacramento Peak Observatory) presented measurements of relative oscillation amplitudes at different positions in the wings of a spectrum line which support Hill's conclusion, but Timothy Brown (High Altitude Observatory) found contradictory evidence from shape changes of the limb darkening function. The issue is currently unresolved.

For many people, the most convincing evidence that the oscillation data arise from genuine dynamical solar vibrations is their phase coherence. Peter Worden (Sacramento Peak Observatory) criticised early analyses of the SCLERA data, but Thomas Caudell (University of Arizona) presented new measurements of solar equatorial diameter variations which, it was finally agreed, convincingly maintained phase over an interval of 22 days. This did not terminate the discussion, however, because as Maurice Gabriel (Université de Liège) pointed out, unless there were a considerable difference in the amplitudes of eastward and westward propagating waves one would not expect phase coherence over a period longer than half the mean rotation period of the Sun. Polar diameter measurements, which have not yet been analysed, are not subject to this criticism.

One of the most exciting aspects of solar oscillations is their potential for providing diagnostics of the solar interior. To realise this potential it is essential to examine the theory quite meticulously to ensure that the physics is well understood, and that measurable properties of the oscillations of theoretical models can be computed accurately. In this respect greatest attention has been paid to the 5-min oscillations, because it is of these that the most refined measurements have been made. Investigations by groups at the University of California at Los Angeles and the Observatoire de Nice have revealed that of the uncertainties beneath the photosphere only the value of the adiabat deep in the convection zone substantially influences the oscillation frequencies; in addition, the Nice group have found that the frequencies of all but the chromospheric

modes are insensitive to variations in the structure adopted for the solar atmosphere, within the framework of the usual linearised theory. The results of both groups seem to imply that the adiabat must be that of a convection zone whose depth is at least 20% of the solar radius. This conclusion is similar to the findings of Beckers and Gilman, who reported last September at the EPS Workshop on Solar Rotation in Catania (*Publication No. 162 of the Astrophysical Observatory of Catania* (Eds Belvedere & Paternò) 1978) that they could not explain the observed absence of a polar vortex unless the depth of the convection zone were at least of the order of 40% of the Sun's radius.

The case for so deep a convection zone is not completely closed. Participants of the workshop were reminded of the EPS conference on solar physics (*Pleins feux sur la physique solaire* (Ed Rösch) CNRS, Paris, 1978) held in Toulouse last year, where Dziembowski and Pamjatnykh pointed out that the observations by Hill and Caudell (*Mon. Not. R. astron. Soc.* **186**, 327; 1979), apparently of solar g modes of degree about 30, are difficult to explain in terms of the so-called standard solar model (see *Nature*, **274**, 739; 1978). At the Arizona workshop Jørgen Christensen-Dalsgaard (Université de Liège) presented computations of g modes in a solar model with low interior heavy element abundance Z ; such models have shallow convection zones through which modes of the kind reported by Hill and Caudell can penetrate with ease. Solar models with low Z also predict low neutrino fluxes in agreement with Davis's measurements, but they do pose many problems, such as how to explain the frequencies of the 5-min oscillations. Ross Rosenwald (University of Arizona) pointed out that if the claim of the SCLERA group concerning the nonlinear behaviour of the oscillations high in the solar atmosphere were correct, the linear calculations performed to date may not be relevant, and this problem may disappear. The claim has not yet been substantiated.

Another new observation which may shed light on this issue was reported by George Isaak (University of Birmingham). His group has measured variations in the Doppler shift of a sodium line in light integrated from the entire solar disk, and have measured discrete frequencies of what appear to be acoustic oscillations of low degree with periods of about 5 min. Unlike the most common 5-min modes, these penetrate beneath the convection zone,

Douglas Gough is in the Department of Applied Mathematics and Theoretical Physics, University of Cambridge, and is at present at the Observatoire de Nice.

and provide an integral measure of the structure deep in the solar interior. A preliminary theoretical analysis favoured a model with a somewhat lower value of Z than that of the standard model, and a shallower convection zone. This model lies between the two extremes discussed above, and so serves to remind us how uncertain we are of the Sun's internal structure.

Degenerate variables

The final day of the meeting was devoted to degenerate variables. Edward Robinson (University of Texas at Austin) gave a stimulating review of the observations, many of which have been obtained only in the past few years. Most of these variables appear to be DA white dwarfs lying in a narrow range of spectral type with $B-V \approx 0.2$, though John McGraw (University of Arizona) in particular has observed variable white dwarfs of different colours. Of the DA dwarfs, about 25% are observed to be variable, and aside from their variability show no other distinguishing feature. Luminosity amplitudes range from a few tenths of a magnitude down to the limit of detectability.

The low amplitude variables have stable periods; one such star, R548 is even more stable than the Crab pulsar. The larger the amplitude the longer the period, and the less stable the power spectrum of the pulsations. It is not unusual for the stars with larger amplitudes also to switch entirely from one mode to another.

Oscillation periods range between about 100 s and 1,000 s, which are much too long to be p modes. Explanations in terms of g modes have been attempted, but it is sometimes difficult to fit the periods satisfactorily. Moreover, with the longer period variables it is difficult to explain why neighbouring g modes in the densely spaced spectrum are not observed, a problem faced also by those who argue that the 2^h 40^{min} oscillation of the Sun is a g mode. Carl Hansen (Joint Institute for Laboratory Astrophysics) suggested that perhaps the oscillations were toroidal elastic modes of a rather mushy material, but reliable estimates of the elastic properties of these degenerate stars are not available to test this hypothesis. In any case it was difficult to explain why only oscillations of the periods observed should be driven, and the others damped. Arthur Cox pointed out that (with the eye of faith) one could imagine the region in the HR diagram where pulsating white dwarfs have been found to be an extension of the classical Cepheid instability strip. He found models that were unstable to radial pulsations, but the periods of such modes are only about 1 s. □

More reliable counts of chromosomal aberrations

from John R. K. Savage

A NOVEL application of a staining method widely used to identify newly-synthesised DNA to the problem of obtaining reliable dose-response curves for the effects of radiation damage in cells is reported in this issue of *Nature* (page 756). The number of chromosomal aberrations induced per cell is the usual measure of radiation exposure. But the precise correlation of dose with the number of chromosomal aberrations it produces is complicated by (amongst other factors) the difficulty of differentiating between cells which have divided a second time after treatment and before analysis. The inclusion of these second division cells in the total cell count inevitably leads to an underestimate of the number of chromosome aberrations produced by any given dose, as the probability of any cell's surviving a second division decreases the larger the number of aberrations it carries. Thus there is selection for less-damaged cells which dilute the scoring sample and reduce the observed yield of aberrations per cell. In a desynchronising cell population like the *in vitro* blood lymphocyte system, the contamination by second and subsequent division cells will increase progressively with time from initiation and a concomitant fall in the yield of asymmetrical aberrations will be observed.

John R. K. Savage is Head of the Cytogenetics Department, MRC Radiobiology Department, Harwell.

In the past, many workers, aware of this problem, have sampled as early as possible after stimulation, on the principle that the earliest samples are purer first divisions. In practice, a compromise is made to ensure that a sufficient number of mitoses for scoring is present, and for human lymphocytes a time ~ 48 h after exposure is usually chosen. Even at this time, second division contamination may not always be negligible and careful workers attempt a further purification of this sample by omitting from their score cells with obviously modified aberrations or those lacking a full complement of acentric fragments.

Now, as Scott and Lyons elegantly demonstrate (page 756) application of the FPG 'harlequin' technique goes a long way towards solving this problem. The technique provides differential staining of the chromatids in second and subsequent division cells based on the semi-conservative segregation of bromodeoxyuridine incorporated in the DNA during synthesis phase. Consequently, by confining scoring to cells with chromosomes not showing differential staining, only first post-treatment division cells will be included in the sample, irrespective of sampling time. As Scott *et al.* show, the asymmetrical chromosome-type aberration yield induced in these cells by 200 rad X-rays is constant, independent of sampling time over the range of 40-72 h. This supplies some evidence for the homogeneous radiosensitivity of

the initial population, and provided the constant yield holds for other doses (which seems to be the case from our own preliminary work), the form of dose-response curves obtained with this method should be much more consistent than hitherto. No enhancement of aberration yield was recorded at the concentration of bromodeoxyuridine used or from its method of application. There was, however, a concentration-dependent perturbation of cell progress, but this has little relevance if the primary population is really homogeneous.

The technique is essentially very simple to apply, and there is no reason why it should not be routinely used in all future dose-response curve work. When one considers the tremendous mathematical effort which goes into the fitting and parameter derivation from such curves and their interpretation, it is surely worth-while to ensure that they have a reliable shape before starting.

The advantages of the method are not confined to dose-response curves; one can see many applications in the field of chromosomal aberration studies. For example, in the study of chromosomal mosaics (individuals whose tissues contain mixtures of two or more karyotypically different cell types) the observed relative frequencies of the cell types are in many cases influenced by selection at cell division. Confining scoring to first division cells may help towards reducing the between-sample variability frequently found.

Are protons unstable?

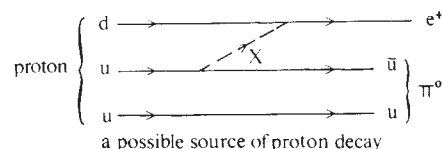
from F. E. Close

THE experimental lower limit on the proton lifetime is well over a trillion times the age of the Universe and this has led people to believe that the proton is indeed absolutely stable. Recent theoretical attempts to construct theories that unify the strong force with the weak-electromagnetic force (see *Nature* 277, 349; 1979), however, have the consequence that the proton is not absolutely stable. A lifetime as 'short' as 10^{31} years could be possible (about an order of magnitude greater than the present lower limit).

Quantum electrodynamics (QED) and quantum chromodynamics (QCD) (the theory of the strong interaction) are very similar field theories and appear in many ways to be profoundly and intimately related. Recently devel-

oped ideas on grand unification of the natural forces do just this and postulate that they are related in a way that is made precise by group theory. Mathematically, QED is a U(1) field theory and QCD is an SU(3) ('non Abelian') field theory, the U(1) essentially displaying the fact that there is but one kind of electrical charge (which can be positive or negative like the set of real numbers) and the SU(3) displaying the existence of three kinds of colour charge (often called red, yellow and blue by analogy with the primary colours). In a nutshell, QCD is like QED with 3×3 matrices in place of real numbers in the 'photon' (coloured gluon) couplings. (Photons are the quanta of the electromagnetic force: coloured gluons those of the strong interaction.) To unify these, find a group G which contains $SU(3) \times U(1)$

F. E. Close is at the Rutherford Laboratory.



a possible source of proton decay

and postulate that there exists a corresponding field theory. The SU(3) QCD and U(1) QED will then be two particular subclasses of this grand field theory. Unification of QCD with the electromagnetic and weak interaction can be achieved if G is the group SU(5) or SO(10). A consequence of this unification is that at energies typical of the world about us the SU(3) colour force is stronger than the U(1) electromagnetic. This is in accord with observed atomic structure: the protons and neutrons (quark systems) are bound in the nucleus by the strong force while the electron (lepton) orbits the nucleus at large distances held by the electromagnetic force.

An outcome of such a unification is that in addition to the photon and the

coloured gluons of QED and QCD, there will exist a new ultraweak force whose quanta carry and couple both to electrical and to colour charge. These quanta have been called 'leptoquarks' because they have the remarkable property of being able to cause quarks to change into leptons, and hence to make the proton decay.

Leptons and quarks are very similar, the only essential difference being that quarks have colour whereas leptons do not. Imagine the effect of a leptoquark quantum being absorbed by a lepton (the electron for example). The leptoquark couples to electrical charge and so can fuse with the electrically charged electron. But the leptoquark also carries colour and so 'paints' the electron transforming it into a quark. The leptoquark quanta carry electrical charge which are fractions of an electron charge so the quark produced from the lepton will have fractional charge, as it must.

Just as electrons could be turned into quarks so could quarks decay into leptons, and this is the source of the predicted instability of the proton. The specific nature of the predicted decay products tends to be rather dependent on the particular model under consideration. In the SU(5) scheme a final state of an antielectron (positron, e^+) and neutral pion (π^0) is predicted and seems to be the one most widely favoured by theorists. The way that this happens is illustrated in the figure and is due to the predicted leptoquark quantum, X. This has electrical charge $4/3$ and can transform a u(up) quark (charge $2/3$) into an antiu ($\bar{u}$) of charge $-2/3$ on being emitted. Absorbed by a d(down) quark of charge $-1/3$ it produces an antielectron (e^+) of charge $+1$. Colour and electrical charge are conserved throughout and the proton (two up quarks and a down) decays into $u\bar{u}$ (π^0) and e^+ at a rate of 1 in about 10^{31} to 10^{33} years.

Experiments that may be sensitive to such decays are now being planned and one is already underway in Montana, USA. If one hopes to detect at least 1 such decay per year then over 10^{33} protons are needed for study, hence over 3,000 tons of material are called for. The cheapest is water and typical experiments plan to have a large swimming pool of about 20 m in each direction, built deep underground to reduce cosmic ray backgrounds. Deep mines are one possibility and in Europe the Mont Blanc tunnel (on average 3,000 metres below 'ground') has been suggested. Detectors of Cerenkov radiation are needed; the signal being some 500 MeV of radiation detected in one direction in coincidence with 500 MeV in the opposite direction. One set will be from the antielectron in the proton decay, the other will be from

the π^0 (this having decayed into two photons which in turn produce electron-antielectron pairs, these latter giving rise to the Cerenkov light).

There are many technical experimental problems to be overcome but the idea seems feasible and the stakes are high. Typically two years preparation and three years experimentation may be involved. However, the experiment currently in progress in the USA may be sensitive to about 10^{31} years' lifetime and could produce results in a year or so. If the lowest theoretical estimates are correct then we may soon have evidence for proton decay. □

Adsorbates on transition metals

from Marvin L. Cohen

THE recent renaissance in surface science has been motivated partly by a desire to explain and exploit the catalytic properties of d-electrons near transition metal surfaces. However, many technologically relevant problems connected with catalysis were put aside to await reproducible experiments and extensions of theoretical techniques which could deal with the properties of clean surfaces and surfaces with adsorbates. Experimental developments over the past 5 years in high vacuum science, photoelectron and electron loss spectroscopy, and low energy electron diffraction have provided accurate data. On the theoretical side, very recent progress has produced calculated spectra suitable for comparison with experiment, but much of the theoretical emphasis has been on semiconductors (Appelbaum & Hamann *Rev. Mod. Phys.* **48**, 3; 1976; Schlüter, Chelikovsky, Louie & Cohen *Phys. Rev.* **B12**, 4200; 1975) where the electronic states of interest have not been d-states.

The semiconductor research has provided convenient tests of the theory. One major point has become clear. A surface is not just the undeformed edge of a perfect crystal. Rearrangements take place, and the electronic charge distorts in response to the surface perturbation. The readjustment of the electronic charge density causes a change in the electrostatic potential felt by the electrons near the surface. This change has to be included in the theoretical calculations. This is done through a self-consistent or feed-back technique. The electronic charge density is calculated for an ideal surface, and the change in the potential arising from the surface redistribution of charge is fed back through the potential to produce a new charge density. This

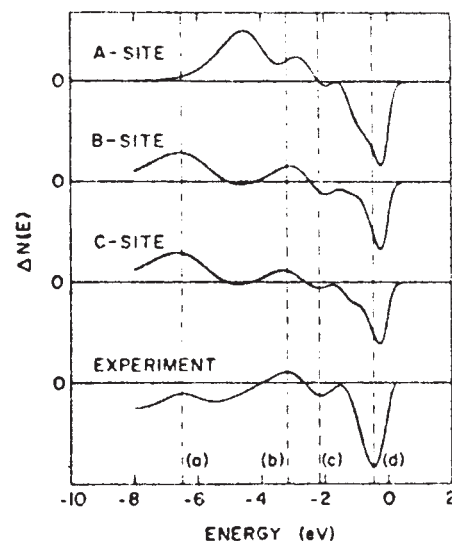


Fig. 1 Comparison of the calculated H-induced photoemission difference spectra with the experimental difference curve from Demuth *op. cit.*

is repeated until the input and output charge densities agree. When the calculation is self-consistent, the detailed surface properties can be examined. Many surface properties are determined by electronic surface states which are found localised near the surface. The surface states are affected by adsorbates, defects, steps and the detailed crystal structure of the surface. Self-consistent calculations for semiconductors have yielded a significant amount of information about these cases.

For transition metals, difficulties in handling the localised d-electrons have resulted in slower progress. However, S. G. Louie (*Phys. Rev. Lett.* **42**, 476; 1979) has recently completed the first fully self-consistent calculation for the electronic structure of an adsorbate on a transition metal. His work focused on the interaction of hydrogen with the Pd (111) surface. This calculation should serve as a model for future adsorbate studies on d-band materials. It also provides useful information for hydrogen-storage technology.

Louie's calculation is based on a self-consistent pseudopotential approach. The pseudopotential is an effective potential which determines the electron-ion interaction in the crystal. The self-consistency allows for charge readjustment at the surface and for charge flow between the adsorbate and the transition metal. This approach had already been used successfully for three studies of clean transition metal surfaces, Nb (001) (Louie *et al. Phys. Rev.* **B15**, 5627; 1977), Pd (111) (Louie *Phys. Rev. Lett.* **40**, 1525; 1978) and Mo (001) (Kerker, Ho & Cohen *Phys. Rev.* **B18**, 5473; 1978). The new extension which adds the hydrogen adsorbate uses the clean surface results

FLOWERS provide nectar for bees, and in return a bee acts as a kind of flying penis, carrying pollen from one plant to fertilise the ovaries of another. Plants and their pollinators are a classic example of mutualism: they have coevolved through evolutionary time in a reciprocal beneficial relationship. However this superficially harmonious view may conceal the true nature of the interaction. It is perhaps more accurate to think of bees having evolved towards efficient exploitation of plants as a food source, while plants have evolved adaptations to minimise the price they pay for getting bees to transfer pollen. G. H. Pyke (*Oecologia* **36**, 281; 1978) has used this line of argument to develop a new insight into the structure of certain inflorescences and the foraging behaviour of bees. He studied three plant genera *Delphinium*, *Aconitum*, and *Epilobium*, all of which are cross-fertilised by bumblebees (*Bombus* spp.), and have their flowers arranged in a vertical spike.

Bumblebees feeding on these plants follow a characteristic movement pattern. They almost invariably start at the bottom of an inflorescence, move up the spike, and leave to fly to the next plant before reaching the top. Within the inflorescence, a bee typically moves vertically upwards from one flower to the nearest one above. The flowers of all three plant genera are arranged in a spiral around the vertical spike, so that by moving vertically upwards, a bee misses out some of the flowers. The bees' movement rules are related to nectar availability. Flowers at the bottom of an inflorescence are older, bigger and contain more nectar than those at the top; hence by starting at the bottom the bee visits the most profitable

Coevolution of bees and flowers

from John R. Krebs

flowers first. As it moves up the inflorescence the bee experiences gradually diminishing returns from the successively smaller flowers, until there comes a point at which more nectar per second could be obtained by travelling to the bottom of the next inflorescence. Pyke's measurements suggested that bees roughly follow this optimal departure rule, and this accounts for the fact that a bee usually leaves before reaching the top of an inflorescence. At first sight one might think that it would pay the bee to visit every single flower on its way up the inflorescence, rather than missing nectar-rich flowers near the bottom. However, the spiral arrangement of flowers reduces the benefit of this movement rule. The extra energetic costs to the bee involved in manoeuvring sideways to follow a spiral path more than offset the benefit of visiting all the flowers. The rule of moving straight upwards gives a higher net energy gain.

Bumblebees seem to have evolved a set of rules for efficient exploitation of nectar, but the plants are equally under an evolutionary pressure to exploit bees, and Pyke suggests that the flower arrangement can be interpreted in this way. The larger, older, nectar-rich flowers at the bottom of an inflorescence are female, while the younger flowers at the top are male (the plants are protandrous hermaphrodites, meaning that each flower turns from male to female as it gets

John R. Krebs is in the Edward Grey Institute of Field Ornithology, University of Oxford.

older). This arrangement of flowers ensures that a visiting bee arrives at the female flowers near the base having just come from the male flowers near the top of the previous plant. In this way the chance of outcrossing is increased, and it is known that in *Delphinium* at least outcrossing results in a higher percentage seed set (Price & Waser *Nature* **277**, 294; 1979). The spiral arrangement of flowers around the stem is also important to the plant. A bee does not usually carry enough pollen to fertilise all the female flowers on a plant, so if it visited every flower it would extract some nectar without providing pollen in return. The plants' evolutionary answer seems to be to arrange its inflorescence in such a way that an efficient bee actually does better by missing some of the female flowers.

Given the design of plants, bumblebees seem to approximate an optimal set of movement rules for maximising net rate of harvesting nectar. At the same time the plants have evolved a design which makes highly efficient (perhaps optimal, but not enough is known about benefits to plants) use of bees as pollinators. It might appear that the coevolutionary struggle has reached a stable point where bees and plants are doing as well as they can, but there is another aspect to the problem. Different species of plants (as well as different individuals of the same species) compete to attract pollinators, and a complete account of the coevolution of bees and plants must be able to explain why different plants living in the same area are designed to offer nectar in different ways. The answer to this sort of question may emerge from approaches such as Pyke's.

for comparison to determine the changes caused by the adsorbate.

A convenient way to explore the effects of the adsorbate is to calculate the surface density of states with and without the adsorbate and to examine the difference in these two functions $\Delta N(E)$. Since the density-of-states function determines the number of electronic states in each energy interval, surface or adsorbate states show up as peaks in this function in the energy interval corresponding to the binding energy of the state. The difference function $\Delta N(E)$ demonstrates how the states near the surface are affected by the adsorbate.

The site where the hydrogen atom is adsorbed on the Pd (111) surface isn't known, but three different sites are likely. Louie's calculation models all three sites (A, B and C) and computes the $\Delta N(E)$ function for each case

(Fig. 1). This function can be compared with a difference photoemission spectrum (Demuth *Surface Sci.* **65**, 369; 1977) to determine which geometry fits the measured results.

One prominent feature common to all the $\Delta N(E)$ curves is the dip near the metal Fermi energy (0 eV). This dip reflects the adsorbate correlated movement of states away from this region to lower energy. The peaks at lower energies arise from the new hydrogen induced states formed from hydrogen 1s and Pd d-states. Comparison of the $\Delta N(E)$ spectra rules out site A and favours B and C which differ little in their environment. Louie concludes that the hydrogen atoms prefer a threefold hollow over the top site. This geometry yields an occupied H-Pd bonding surface band centred at 6.5 eV below the Fermi energy (Fig. 1) in good agreement with experiment

and an unoccupied antibonding H-Pd surface band at high energies (not shown in Fig. 1). Other surface structure is found and analysed.

The features of the H-Pd bonding state can be studied using charge density contour maps. These illustrate the details of the mixing between the hydrogen and Pd orbitals. Louie has also calculated the total electronic charge distribution and finds that some charge spills out into the vacuum above the surface. The values for the number of valence electrons per surface unit cell are 0.2 in the vacuum above the surface and 9.7, 10.1, 10.0, 10.0 for the first, second, third and fourth layers into the bulk (10 is the bulk value). The calculated work function is in excellent agreement with experiment.

Although Louie's calculation only considers a specific adsorbate on a specific face of one transition metal,

his success in getting information about the adsorbate site and bonding configurations provides strong motivation for future studies. The next level of complexity would be studies of molecular adsorbates (for example CO) on different surfaces of a variety of transition metals. Calculations of this kind should be possible soon, and theoretical results on systems like these should provide useful data for understanding surfaces and for developing new catalysts. □

M. L. Cohen is Professor of Physics at the University of California, Berkeley, and at the Lawrence Berkeley Laboratory.

Surface structure by SEXAFS

from D. T. Clark

THE wide variety of techniques which have been developed to take particular advantage of the special characteristics of synchrotron radiation have previously been notified in these columns and (*News and Views* 276, 672; 1978) span fields as diverse as the band structure of metals and the study of time-dependent conformational changes for proteins. The benefits of having a dedicated synchrotron source as opposed to operating in parasitic mode to basic high energy physics experiments has been appreciated for some time in the UK and in consequence a national facility is currently nearing completion at SRC's Daresbury Laboratory. It is already clear from the published work, particularly of a number of research groups in the USA, that synchrotron sources will have a vital role in surface science in particular. The benefits of a highly collimated, continuous spectrum which includes wavelengths not available from other sources is self evident in the investigations of structure and bonding of the surfaces of solids since differential changes in photoionisation cross sections and different sampling depths (consequent upon the strong dependence of electron mean free paths on kinetic energy) are thereby routinely available.

In addition, however, there are three properties of synchrotron radiation sources which enhance their potential for research in surface science. First since the electron beam is extremely stable in energy, position and intensity the light-emitting areas are endowed with the same characteristics. Second the substantial degree of polarisation of the photon source after monochromatisation provides a means of studying

asymmetry parameters and channelling phenomena and finally since the synchrotron source typically operates in the UHV regime there is direct compatibility with the requirements for carrying out experiments on uncontaminated surfaces.

The experiments which have so far been carried out in the area of surface science have largely centred on the investigation of the valence bands of metals and semiconductors and this has been a fruitful area of research particularly in the US in the research groups of Eastman, Spicer and Shirley.

In an important paper recently appearing in *Phys. Rev. Lett.* (42, 104; 1979) Bianconi and Bachrach have shown for the first time that measurements of surface extended X-ray absorption fine structure (SEXAFS!) provides a powerful alternative to LEED in the investigation of surface geometries of single crystals. This obviously extends the scope of synchrotron radiation in the investigation of surfaces and it is worthwhile briefly considering the background to this work.

The basis of EXAFS, in particular as it relates to the investigation of metalloprotein systems, has recently been considered in these columns (*News & Views* 277, 89; 1979) and one need only note that previous theoretical proposals relating to the use of SEXAFS have now been implemented in the paper described here. The important question of the structure determination of surfaces have until now been addressed by one technique only, namely low energy electron diffraction (LEED). The technique is limited to single crystal analysis and the investigation of chemisorbed atoms or molecules with long range order and has relatively poor resolution. Despite the difficulties in theoretically modelling the experimental data the technique has provided important data which illustrate for example the reconstruction (change in interatomic distances) for most semiconductor surfaces.

LEED experiments on Al (100) and Al (111) surfaces have previously been reported (Martin & Samorjai *Phys. Rev.* B7, 3607; 1973; Jepson, Marcus & Jona *Phys. Rev.* B6, 3684; 1972; 5, 3933; 1972) and have been interpreted in terms of no reconstruction for the former and a 5–10% increase in interatomic spacing for the latter face. Since LEED typically provides a resolution of ~ 0.1 Å there is clearly some ambiguity in interpreting small changes in spacings. By contrast Bianconi and Bachrach demonstrate that the substantially higher sensitivity (with respect to spacing) of the EXAFS measurements allows an unambiguous assignment of both the sign and magnitude of the restructuring of the Al

(111) surface compared with the bulk.

The experiments described by Bianconi and Bachrach involved measuring the quantum yield of secondary electrons originating from inelastically scattered LVV Auger electrons generated in the decay of the absorption produced core holes. Using this partial yield technique measurements may be made of the $L_{2,3}$ surface soft X-ray absorption spectrum of a surface layer of aluminium single crystals; the thickness being determined by the effective escape depth of the secondary or Auger electrons with the selected kinetic energy.

The experiments were carried out on the grazing incidence monochromator fitted to the 4° beam line at the Stanford Synchrotron Radiation Laboratory. The photoelectron energy was selected with a cylindrical mirror analyser (detection cone at $\theta=42^\circ$) using a 3 eV window. The linearly p polarised light was incident near grazing ($\theta \leq 10^\circ$) and this strongly emphasises the interatomic distance normal to the surface. The Al single crystals were cleaned by ion sputtering and annealing at 4×10^{-10} Torr and in separate experiments the residual oxygen contamination was shown to be < 0.001 monolayer.

Surface soft X-ray absorption spectra of the Al (100) and Al (111) faces were measured collecting the inelastically scattered Auger electrons at 45 eV and 4 eV. At 45 eV final state energy an average of ~ 2.9 Å thick layer contributes to the spectrum which corresponds effectively to the surface layer since the interatomic spacing is 2.86 Å for the bulk metal. For a 4 eV final state energy the escape depth is closer to 20 Å so that *a priori* one might expect a comparison with data for the bulk. Structural information is extracted from this data by fitting the first large EXAFS modulation. The almost exact correspondence of the data for bulk aluminium and for the Al (100) surface shows conclusively that within the limits of the experiment there is no restructuring for this surface. By contrast the fact that the EXAFS structure shifts towards higher energy on going from bulk to surface shows directly that for the Al (111) face there is a decrease in interatomic spacing. By using the bulk aluminium EXAFS as reference this contraction may be quantified as $\Delta r = 0.15 \pm 0.05$ Å.

These experiments confirm the great potential of SEXAFS in the investigation of the surface structure of single crystals and it will be of interest to have comparisons with LEED data on other materials for which surface restructuring has been inferred. It should be noted that SEXAFS can also in principle be applied to the study of amorphous surfaces and we may antici-

pate that the technique will be extensively applied to such materials over the next few years. □

D. T. Clark is in the Department of Chemistry, University of Durham.

Nuclear giant dipole resonance

from P. E. Hodgson

LONG ago it was found that the cross sections of many reactions of gamma rays with nuclei, in particular those in which a nucleon is ejected, show broad resonances at quite high energies, usually around 20 MeV for light nuclei and falling to about 10 MeV for heavy nuclei. It was soon suggested that these resonances are due to a special type of collective excitation in which the neutrons vibrate against the protons. The resonance was found to be E1 (electric dipole) and a macroscopic calculation based on the liquid drop model gave approximately the correct variation of resonance energy with atomic weight.

Subsequently, detailed microscopic models have been developed that interpret the resonance as due to the coherent superposition of all possible particle-hole excitations from one major shell to the next. This was able to account for the width and the energy of the giant dipole resonances in several light nuclei.

The macroscopic models in terms of neutron and proton fluids were also developed, and these have the advantage that they give results for a whole range of nuclei for which the microscopic calculations would be very complicated. The most detailed of the macroscopic models are first that of Goldhaber and Teller (*Phys. Rev.* **74**, 1046; 1948), which assumes that the oscillations of the neutron and proton fluids each take place within a fixed boundary, and this predicts that the excitation energy varies as $33 A^{-1/6}$. A second model, due to Steinwedel and Jensen (*Z. Naturforsch.* **5A**, 413; 1950) assumes that the neutron-proton

oscillation takes place within one fixed boundary, and this gives $80 A^{-1/3}$ for the energy dependence. More recently, Myers and Swiatecki (*Phys. Rev.* **C15**, 2032; 1977) have developed a more detailed theory based on their droplet model of the nucleus, and this gives an energy variation of $A^{-0.23}$, which is nearer to the experimental results than the other models. The models also predict distinctly different transition charge densities.

To test these models, Pitthan and colleagues at the Naval Postgraduate School, Monterey, California have recently made some careful measurements of the inelastic scattering of electrons by ^{140}Ce . (*Phys. Rev. Lett.* **41**, 1276; 1978). This nucleus was chosen because of all the nuclei investigated it shows the most favourable separation between the various possible resonances. The spectrum of inelastically scattered 91.2 MeV electrons that they obtained is shown in Fig. 1, with the background already subtracted. A number of peaks are visible, corresponding to the electric resonances of various multipolarities. The spectrum is analysed into the contributions from the different multipolarities, and the one of interest for distinguishing between the different models is the dipole resonance at about 15.3 MeV. Similar measurements were made at a number of incident electron energies from 65 to 150 MeV.

The results for the dipole resonances at different electron energies were compared with the models of the excitation process by plotting the ratio of the experimental cross section to the Mott cross section at a particular angle as a function of the momentum transfer, and this is compared with predictions of the three theories in Fig. 2. It is clear that the Myers-Swiatecki model agrees very well with the data, whereas the Steinwedel-Jensen model predicts cross sections that are too high.

The Goldhaber-Teller model predicts cross sections that are too low, but it is just possible that the shortfall could be attributed to the presence of an undetected monopole (breathing mode) resonance. This state, in which the nucleus oscillates radially, has been predicted theoretically, and some evidence for its presence has been found in previous experimental work (see for example *News & Views* **271**, 212; 1978). To study this possibility, the difference between the predictions of the Goldhaber-Teller model and the experimental results was compared with distorted wave calculations of the contribution to be expected from a monopole excitation. The overall dependence

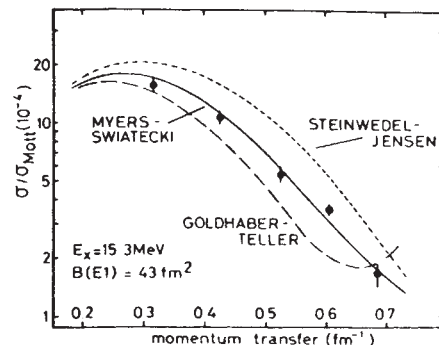


Fig. 2 Comparison between the experimental results of the electric dipole resonance at several values of the momentum transfer and the predictions of three theories of the excitation process.

on momentum transfer is found to be the same, and if it is indeed monopole it exhausts about 45% of the energy-weighted sum rule. This interpretation is however doubtful partly because the variation with A is already in disagreement with the Goldhaber Teller model, and partly because if the monopole interpretation is correct we would expect to see all the energy-weighted sum. Thus at present the evidence favours the Myers-Swiatecki model for the giant dipole resonance. In addition, there is some discrepancy between the evidence in favour of the monopole state obtained from measurements of inelastic alpha-particle scattering and its absence in the more thoroughly understood inelastic electron scattering. Further measurements of both electron and hadron inelastic scattering are needed to resolve this discrepancy. □

Physics in archaeology

from Robert Hedges

TRADITIONALLY, Archaeometry Symposia focus on the development and application of physical methods to archaeology, and there were no papers on environmental or biological issues, although two studies on the survival and extraction of organic residues were presented. Broad categories, often leading to parallel sessions, of dating, prospection, artefact analysis with the aims both of reconstructing ancient technologies, and determining the original point of manufacture, and mining and extractive metallurgy continued to provide the bulk of the research reports.

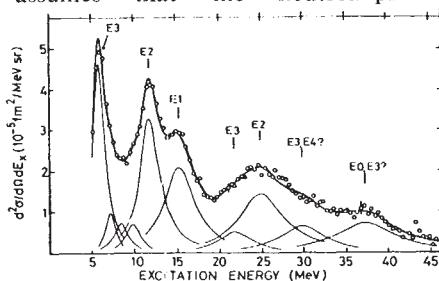


Fig. 1 Spectrum of 92.1 MeV electrons inelastically scattered from ^{140}Ce at 90° , showing the peaks due to the electric resonances of the multipolarities indicated. This spectrum is analysed into its components.

P. E. Hodgson is a Lecturer in Nuclear Physics in the University of Oxford.

*The 19th International Symposium on Archaeometry and Archaeological Prospection was held on 28-31 March in London.

Dating was emphasised by the presentation of three longer reviews, outlining recent progress. D. Walton (University of Oxford and McMaster University) described the measurements made of the strength of the Earth's magnetic field from small samples taken from dated Greek pottery, using a SQUID magnetometer. The resulting curve shows rapid fluctuations in the field strength which, apart from their general interest, he pointed out might eventually be useful for precise dating. This account was nicely contrasted by one from J. Pilcher (University of Belfast) who reviewed the latest story on radiocarbon calibration. Here the rapid fluctuations ('wiggles') in the calibration curve have been a source of contention for several years, but it seems that, with the development of more accurate measurements, an honourable compromise is being reached. The new possibilities opened to radiocarbon dating through the development of detection by accelerators were also reviewed. Several papers were devoted to the dating of calcitic cave deposits from the disequilibrium found in the daughter products of uranium incorporated into the calcite. This approach, which bridges the gap between potassium/argon and radiocarbon dating, is clearly becoming more useful. Technical papers on thermoluminescence dating of pottery, flint and calcite showed that the time when it can provide a problem-free dating service is still some way off. The same also applies to dating by amino acid racemisation.

Research into prospection methods has diminished somewhat over the years, most papers being application reports or describing advances in data-processing techniques. The analysis of artefacts remains a very strong centre of interest, however. The sourcing of such raw materials as jade, obsidian, sanukite, marble, as well as pottery and glass, from measurements of characteristic trace element concentrations (usually by neutron activation) and also of stable isotope ratios were described. The relationship of metal composition to the parent ore also was the subject of discussion, since the smelting process, and especially the addition of fluxes, can complicate this. Fortunately the excavation of mining sites, such as the Bronze Age site of Timna (in the Negev), in which ore, slag, smelted metal and artefacts are all available for study, can add much information to a perennially-disputed area. Although no radically new method or material for determining provenance has been introduced, the quality of work now able to exploit the general principles

R. E. M. Hedges is at the Research Laboratory for Archaeology, Oxford University.

Unified theories?

THE analogy to Maxwell's unification of electricity and magnetism and the so-called 'unified' theory of weak and electromagnetic interactions expressed in F. Close's report in *Nature News and Views* 277, 349; 1979) "an intellectual achievement comparable with Maxwell's unification of electricity and magnetism", is an overstatement. Because however this statement is amply and repeatedly expressed in all journals, and even in the general press, it should be emphasised that the latter theory is not a unified theory on the level of Maxwell's unification. There are two coupling constants G and e of the weak and electromagnetic interactions before the 'unification', and there are still two coupling constants (parameters) after the 'unification', only mixed. Moreover, a large number of new (unobserved) fields are introduced here, but not in Maxwell's case. Two

F. CLOSE REPLIES: In his book 'The First Three Minutes' Weinberg writes: "A field theory which *unifies* [my italics] (weak and electromagnetic) forces was proposed by myself . . . and Salam". It is the continuing accumulation of data supporting this theory that leads me and others to be so optimistic about it. On the other hand I recognise that there are important predictions that are as yet untested, hence my reference to it still as a candidate theory.

If the theory is eventually confirmed to be truly unified (in the sense of involving only one coupling constant,) then I would regard that as an achievement comparable to Maxwell's. That is a personal opinion which Professor Barut might not share. However he is correct to remind us that the *unification* (as defined above) is not yet confirmed

general observations may be made.

(1) Given any two theories, one can always consider them together as part of a larger more symmetric system, if enough new fields (such as gluons, Higgses) are introduced. It is like putting any two broken shapes into a larger more complex or symmetrical figure if enough clay and glue is introduced. (2) A theory is the more renormalisable the more fields are present to cancel the divergences.

Under these circumstances gauge theories can be called unified field theories only if and when all these additional hypothetical gluons and Higgses are found and if there is only one coupling constant. Until then all so-called 'evidence' must remain circumstantial and we should call them simply gauge theories and not unified theories.

A. O. BARUT

International Centre for Theoretical Physics, Trieste

even though no evidence against it has yet been found. The unified theory predicts that charged and neutral weak radiation exist and the corresponding quanta are $W_{\pm}$ and Z bosons with well defined masses. Just as the prediction of electromagnetic radiation was pivotal in electromagnetic theory so are the predictions of the masses of the weak quanta significant tests for the unified theory.

It is true that the properties of the Higgs fields are as yet unclear but I think that Professor Barut exaggerates by claiming that a "large number" of new unobserved fields are introduced. The inclusion of gluons in his list is particularly misleading. These have nothing to do with the weak-electromagnetic unification but are instead the gauge fields of QCD—the candidate theory of the strong force.

already established has considerably improved.

The original technical divisions of archaeology into Stone, Bronze and Iron Ages have become greatly refined as a result of more subtle studies of the materials manufactured in antiquity. Most studies centre on the interpretation of chemical analytical data, generally obtained by non (or minimally) destructive methods. These are enhanced by such sophisticated techniques as ESR, and Mössbauer spectrometry, from which, for example, information about the firing conditions of pottery, and possibly subsequent weathering on burial, is obtained. Several papers were given on coin analyses, as well as considerations on distributions of coin dies. The study of ancient metallurgy bene-

fits greatly from the information available from metallography. Thus we were able to consider how much the workers of Early Dynastic Egypt knew of the work-hardening properties of their copper tools, and how much Mediaeval armourers understood of the tempering properties of their steels. Modern experiments with reconstructed bows have confirmed theories of armour-piercing, and show that Mediaeval craftsmen, while perhaps not aware of the theory, nevertheless achieved optimum design in practice.

The overall impression left was of an encouraging increase in the quality of work presented. On the whole the archaeology considered was more appropriate and interpretations better judged. □

review article

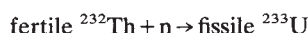
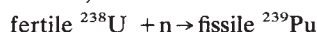
The use of high energy accelerators in the nuclear fuel cycle

P. Grand

Department of Nuclear Energy, Brookhaven National Laboratory, Associated Universities Inc., Upton, New York 11973

Nuclear power is at present derived from the burning of ^{235}U which constitutes about 0.7% of the natural uranium resource. A long-term supply of nuclear fuel for electrical power generation would require breeders to convert ^{238}U , or ^{232}Th , into fissile material. Accelerator breeders offer an alternative to the fast breeder reactor for this conversion.

THE nuclear-power industry in most of the world is based at present on light-water-cooled thermal reactors (LWRs) either of the pressurised water or the boiling water type. These reactors have proved to be reliable and economical; they supply more than 10% of the electric power generated in the US. In the present nuclear-fuel economy, LWRs burn naturally occurring fissile uranium (^{235}U) concentrated to about 3% of the total fuel volume; the remaining fuel consists of the element ^{238}U . Isotope ^{238}U is called 'fertile' because it can be converted to fissile plutonium (^{239}Pu) which can then be used as a nuclear fuel; thorium (^{232}Th) is also fertile. Conversion from fertile to fissile material is accomplished by neutron capture in fertile nuclei. Thus, in simplified form,



This conversion occurs in every reactor. LWRs have a conversion ratio (fissile material created to fissile material burned) of about 0.6. If this ratio can be made larger than 1, the reactor breeds: it produces more fuel than it burns.

Natural uranium contains only 0.7% fissile ^{235}U , the remainder being ^{238}U . To achieve the ~3% ^{235}U concentration required for LWR fuel, mined uranium is processed in an isotopic separation plant. About 6 tonnes of natural uranium are required to produce one tonne of fuel at 3% concentration. The remaining 5 tonnes, still containing about 0.2% ^{235}U , accumulate at separation plants as waste. The 1 tonne of 3% enriched uranium produces about 2.3×10^8 kWh of electrical energy ($30,000 \text{ MW d}^{-1} \text{ tonne}^{-1}$ (thermal)) in an LWR.

If we assume the useful life of a 1,000 MW(e) nuclear reactor to be 30 yr, its fuel requirements will be about 6,000 tonnes of natural uranium over that period, of which only 1,000 tonnes will go through the reactor burn cycle and end up as spent fuel. Spent fuel still contains ~2% fissile material, about half of which is plutonium and the remainder unburned ^{235}U . Approximately 30% less fuel would be needed were the ^{239}Pu recovered from the spent fuel by chemical reprocessing.

The natural uranium resource in the US has been estimated to be anywhere from 1.5 to 4 M tonnes (refs 1, 2). These estimates include uranium which can be recovered at a cost of less than \$30 per pound of yellow cake (U_3O_8). This resource can only support 250,000–600,000 MW(e) respectively of nuclear power generation capacity based on present once-through LWR fuel cycle. Domestic resources in the US would be sufficient to supply this country's foreseeable power needs well into the twenty-first century using only the once through LWR cycle. However, many other countries, having little or no uranium resources, are not so fortunate. Therefore, the present generation of LWRs, operating on the fuel cycle described here, is not a long-term solution to the world electrical energy problem.

The development and commercialisation of the breeder reactor has been described as the answer to the full use of the world's

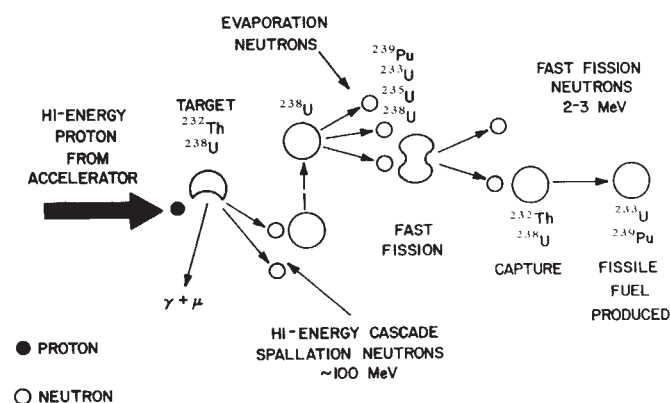


Fig. 1 Nuclear reactions produced in the accelerator breeder target.

uranium resources. As the breeder reactor has a breeding ratio greater than 1, essentially all the naturally occurring fertile ^{238}U in the fuel element could be rendered fissile while at the same time power was produced. Using the breeder reactor, the uranium fuel resource could be extended 100 times, and with higher priced reserves becoming economical, an almost unlimited energy source would become available. However, breeder reactor development has been slower and costlier than first estimated. In addition the concomitant chemical reprocessing facilities, are seen as presenting a serious risk of nuclear weapons proliferation. As such, the desirability of the breeder-reactor fuel cycle is now being seriously questioned. Other reactor types have near-breeding characteristics, such as the CANDU thorium cycle, and the gas-cooled reactor which also uses ^{233}U fuel. These reactors can stretch the fuel resource, but their fuel cycles have not been developed to the same extent as that of the liquid-metal cooled fast breeder reactor.

Accelerator breeding provides an alternative means of greatly extending the natural uranium fuel resource^{3,4}. It can produce the fissile fuel for present-day, well-developed light water reactors, whilst maintaining the high proliferation resistance of the present fuel cycle.

The background to accelerator breeding

The growth of accelerator technology can be attributed wholly to government funding for basic research in nuclear and elementary particle physics over the past 30 yr. Among the many types of accelerators developed, one in particular offers the potential to accelerate large beam currents (many mA)

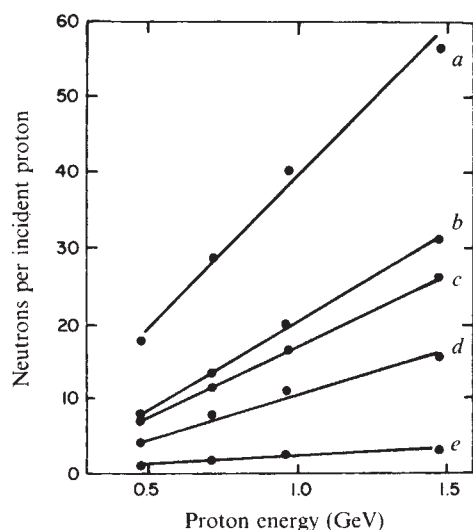


Fig. 2 Measured yield of neutrons by bombardment of a heavy metal target with high energy protons. *a*, U, 10.2 cm diameter $\times$ 61 cm; *b*, Pb, 20.4 cm diameter $\times$ 61 cm; *c*, Pb, 10.2 cm diameter $\times$ 61 cm; *d*, Gn, 10.2 cm diameter $\times$ 61 cm; *e*, Be, 10.2 cm $\times$ 91.6 cm.

continuously to very high energies (thousands of MeV)—the linear accelerator^{5,6}. A linear accelerator added to the nuclear fuel cycle makes a different method of producing fissile material possible. This uses the neutrons produced by a nuclear reaction in the target struck by the high energy beam.

At very high energies, charged particles (in this case protons or deuterons generated by the accelerator) interact with the target material, mainly through nuclear inelastic collisions.

When the particle hits a complex nucleus, nucleons are ripped off, or spalled from the nucleus. The energy of the spallation products is sufficient to induce additional spallation in an intra- or inter-nuclear cascade^{7,8}. Ultimately, the energy of the incident particle not carried away by the escaping particles will be shared by the remaining nucleons of the target nuclei leaving the residual nuclei in a highly excited state. This is followed by a statistical evaporation process in which nucleons and γ rays are emitted until the nuclei are de-excited. Thus, neutron multiplication occurs in any target material. Heavy materials, however, will result in larger neutron yield. Additional neutron multiplication will occur in fissile materials due to the fast fission process⁹. Figure 1 shows the processes involved in a uranium or thorium target struck by a high energy proton. Figure 2 shows measured values of neutron multiplication for targets of different materials and given geometry at different proton energies¹⁰.

The earliest exploration into the use of accelerators to produce fissile materials was made by a group at Berkeley in the early 1950s. The device was called the MTA (materials testing accelerator¹¹). The objective was to produce plutonium for the weapons programme from the tails low in ^{235}U accumulating at the Oak Ridge diffusion plant. The feed to the separation plant at the time was mostly uranium from abroad, principally the Belgian Congo and South Africa. If the diffusion-plant tails could have been turned into plutonium, this would have freed the US from dependence on a foreign source of uranium. The project was abandoned when substantial uranium deposits were discovered in the western US. Construction of the accelerator had already begun when the MTA project was ended in 1954, and an accelerator prototype had operated successfully.

In 1952, Lewis, in Canada, had considered the idea for the production of power¹², and in the 1960s, the Canadian concept had evolved into the intense neutron generator (ING) which would have supplied an intense neutron source for research¹³. Although the project was not funded because of financial constraints the Canadians have continued development of the accelerator breeder and its use in the Canadian CANDU reactor fuel cycle¹⁴. Recently, interest has grown because of the success of new linear accelerator designs and the interest in alternative ways of producing nuclear power and nuclear fuels. This led to a 1977 symposium¹⁵ held at Brookhaven National Laboratory¹⁵, which coincided with increased concern over risks of proliferation of nuclear weapons.

Research status and system outline

Present interest in accelerator breeders is mainly concentrated in North America. A sustained programme has been continued for years at Chalk River, Canada. The Canadian team has worked on all aspects of the accelerator breeder as a producer of fissile ^{233}U from thorium to fuel CANDU reactors. Since the CANDU reactor burning ^{233}U , has near-breeding characteristics (conversion ratio ≥ 0.9) a single 0.3 A–1 GeV accelerator breeder could supply fuel for about 10 reactors. This fuel cycle does, however, require chemical reprocessing like that of the breeder reactor, but this fuel cycle also makes perhaps the most efficient use of the accelerator breeder.

The work carried out at Chalk River includes studies, development, and prototyping of new accelerator structures, detailed calculations and experimental validation of target neutronics, and system studies within the context of the Canadian nuclear power programme.

Los Alamos Scientific Laboratory plans to undertake a major experimental programme at the 800 MeV proton accelerator, LAMPF (linear accelerator meson physics facility) to study breeding, target neutron yield, and fissile material production rates. Oak Ridge and Argonne National Laboratories have had small feasibility study programmes dealing mostly with neutronics aspects, systems and economics.

Finally, Brookhaven National Laboratory has a programme to study feasibility of the accelerator breeder and its economic desirability within the context of US policy of a proliferation-resistant fuel cycle. There is also the intention to produce fuel for existing LWRs¹⁶. In this sense the approach is quite different from that taken by the Canadians. The Brookhaven study has yielded two highly proliferation-resistant nuclear fuel cycles showing promise in terms of technical feasibility and economic desirability.

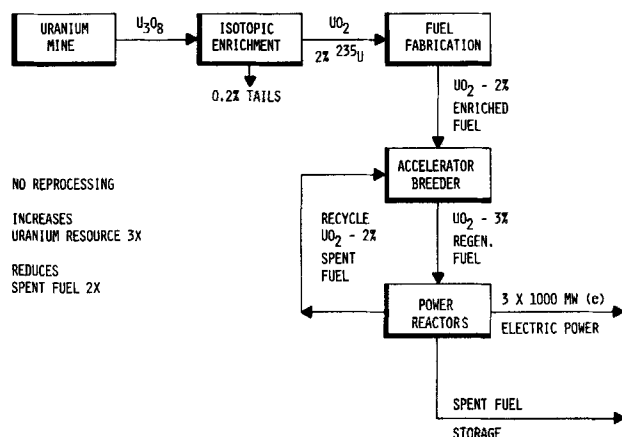


Fig. 3 Linear accelerator fuel regenerator nuclear fuel cycle.

Figure 3 shows the linear accelerator fuel enricher regenerator (LAFER) fuel cycle. It is called an enricher regenerator because its main function is the topping up of the initial fuel enrichment before burning and to rejuvenate the burned or spent fuel elements discharged from the reactor to make possible a second burn cycle. Thus, fuel assemblies that presently are enriched to $\sim 3\%$ ^{235}U and burned to $30,000 \text{ MWD tonne}^{-1}$ could yield $60,000 \text{ MWD tonne}^{-1}$ with an initial enrichment of only 2% . No reprocessing of fuel is involved. This scenario would require 1 LAFER for each 3 LWRs, the LAFER being a $0.3 \text{ A}-1.5 \text{ GeV}$ linear accelerator with a calculated annual production of 1.1 tonnes of fissile material in conventional LWR fuel assemblies.

In principle, one could consider irradiating fuel assemblies in the LAFER through more than two cycles, with correspondingly better fuel utilisation and better economics. However, uncertainties concerning the effects of fission product buildup, and of radiation and corrosion damage to materials indicate that we should not consider more than about $60,000 \text{ MWD tonne}^{-1}$ burn-up at present.

The natural uranium requirement to fuel an LWR operating in conjunction with a LAFER is calculated to be $1,750 \text{ tonnes}$ over its 30-yr life. This is about 3 times less than the 6000 tonnes presently required. Also the rate of generation of spent fuel is only half that of the conventional fuel cycle.

Another proliferation-resistant, accelerator-breeder fuel cycle is shown in Fig. 4. Here, the accelerator re-enriches spent fuel discharged from an LWR back to the fissile concentration required for burning. The fuel assemblies are then dismantled and refabricated without separation of the fissile material component of the fuel. Thus, reprocessing in this case removes the high vapour pressure fission products only. No stream of highly enriched or pure fissile material is ever present. And as the fuel is dilute and radioactive at all times, there would be little or no risk of theft. The fuel is then burned again in the conventional LWR. This approach to the accelerator-breeder fuel cycle has obvious advantages. Like the breeder reactor, it increases the uranium resource availability whilst remaining within the well proved technology of existing light-water cooled

reactors. Here again, one accelerator breeder would be required to support three $1,000 \text{ MW(e)}$ power reactors.

The laboratories involved in these studies seem to agree that the linear accelerator technology for this application is well in hand and that the major technical problems reside with the target system. These problems concern the ability to optimise neutron multiplication and capture (the fissile fuel production rate) in the presence of severe engineering constraints such as radiation damage to materials, power dissipation and so on. However, substantial progress has been achieved during the past year and accelerator breeders are not only possible but could be built and demonstrated at a reasonable cost and within a period of around 10 years.

Brookhaven facility

The most advanced facility design is that developed at Brookhaven National Laboratory. This facility would consist of two distinct parts: a $0.3 \text{ A}-1.5 \text{ GeV}$ linear accelerator, or linac, and its associated target-blanket assembly with power generation system.

The head-end of the linear accelerator would consist of an Alvarez drift-tube linac¹⁷, operating at a radio frequency of about 200 MHz up to an energy of 150 MeV . The Alvarez structure would be followed by a so-called $\pi/2$ mode disk-and-washer loaded waveguide structure, up to the final energy. This type of structure has been developed successfully in the USSR¹⁸. An acceleration rate of 1.5 MeV^{-1} seems close to optimum. The 1.5 GeV linac is about 1000 m long. The design of the accelerator lies well within present capabilities and no fundamental

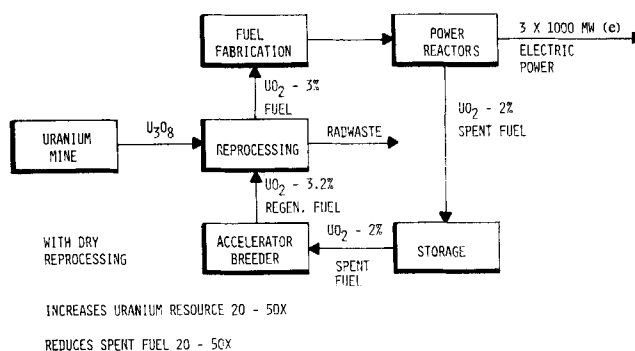


Fig. 4 Linear accelerator fuel producer nuclear fuel cycle (with reprocessing).

problems are anticipated. Experience with linear accelerators indicates that such machines can be operated without appreciable beam loss during acceleration, so that residual radiation will not handicap maintenance of the machine.

The distance between the target system and the accelerator is about 100 m . This drift length, containing isolation valves and instrumentation, will keep the accelerator free of any contamination by the high-radiation target area. Figure 5 shows the design of the target. It consists of a primary lead-bismuth target, stopping the entire proton beam, and of a secondary target (blanket) containing the fertile uranium material. The primary target consists of falling liquid lead-bismuth columns or jets arranged to provide an evenly distributed neutron source. This is accomplished by providing a variable target density with respect to target depth, and by stepping the target to intercept different parts of the proton beam at different points within the neutron source area. The liquid-bismuth jets operate in the

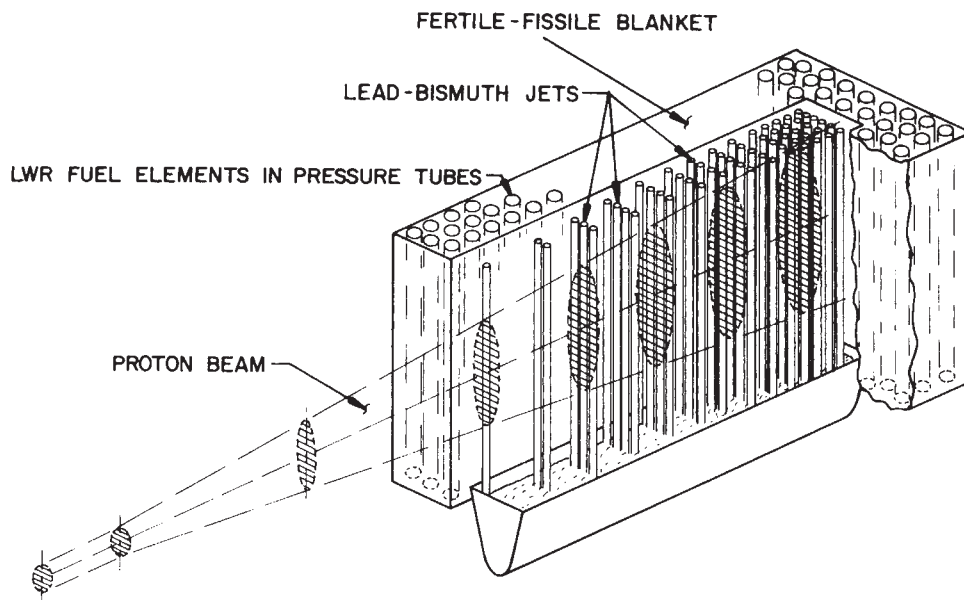


Fig. 5 Accelerator breeder target-blanket concept.

vacuum of the containment vessel, which is directly connected to the accelerator by the beam transport system. No window material is required between the accelerator and the target. The uranium fertile material in the blanket consists of LWR fuel assemblies located in individual pressure-tubes. These surround the primary target neutron source in a manner consistent with minimisation of neutron leakage, parasitic absorption and mechanical design constraints. The assemblies of fuel, coolant and moderator are designed to remain highly subcritical in any circumstance. During an irradiation cycle, fuel shuffling is required to achieve good control of reactivity buildup. The neutron multiplication due to fast fission in the blanket produces thermal energy. This energy, as well as that generated by the proton beam in the lead-bismuth target, is used to generate electrical power by a conventional steam-turbine system. The safety considerations applicable to the target-blanket system are the same as those for an LWR, with the notable exception that the target of the accelerator-breeder is subcritical. However, the entire target-blanket and primary coolant systems are in a containment building similar to that of a conventional power reactor with the same safety features.

Economics and future prospects

Economic analyses carried out at Brookhaven and elsewhere indicate that the cost of fuel produced by an accelerator breeder is high, between \$200 and \$300 per gramme of net fissile fuel produced. This compares with the present cost of $< \$100 \text{ g}^{-1}$ of net ^{235}U burned in LWRs.

A better indication of the accelerator breeder economic prospects is obtained by looking at the entire nuclear fuel cycle cost, or rather, the cost of electric power to the consumer. On that basis, the consumer power cost was calculated using the accelerator breeder in conjunction with LWRs as shown in Figs 3 and 4. It was found that the cost per kWh would increase by

about 25%. At present, therefore, the accelerator breeder cannot compete on a strict economic short-term basis with the other means available to produce the fuel required for power reactors, namely the mining and enrichment of natural uranium. But will things change in the future?

The projected scarcity of uranium had led to the development of the breeder, and the cost of electricity produced by the breeder fuel cycle will be higher than what we are now paying (notwithstanding inflation). The accelerator-breeder-LWR fuel cycle cost may be competitive with the reactor breeder fuel cycle cost. There are also other cost parameters more difficult to assess. For example, what are the cost benefits of the continuing exploitation of the same, and well developed, LWR technology, of the inherent proliferation resistance of the fuel cycle using the accelerator breeder, of the environmental impact of decreased mining activity (especially as we move to lower yield ore bodies) and of the ability to use spent fuel now being stored indefinitely in storage pools?

Also, projections of nuclear fuel cycle cost are clouded with many uncertainties such as: projected cost of U_3O_8 , new licensing requirements for plant safety, spent fuel storage and waste disposal, safety problems specific to the breeder reactor, cost and social desirability of the nuclear fuel cycle of the future, and so on.

The economic picture painted here is one of confusion. It points out the many difficulties at arriving at an objective cost-benefit analysis and projecting the potential of the accelerator breeder in the nuclear fuel cycle, or of any other competing system as well¹⁹. We can conclude however, that accelerator breeding offers a real alternative to the breeder reactor. It does so while retaining the present safety of the existing LWR based nuclear fuel cycle. Accelerator breeders are an extension of existing technologies, and hence can be developed at a reasonable cost and could be used commercially within the next 20 years.

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articles

IUE observations of absorption by hot gas in the nebula NGC6888

M. C. E. Huber & H. Nussbaumer

Atomic Physics and Astrophysics Group, ETH-Zentrum, Zurich, Switzerland

L. J. Smith, A. J. Willis & R. Wilson

Department of Physics and Astronomy, University College London, Gower Street, London WC1, UK

New UV observations of Wolf-Rayet stars obtained with the IUE satellite show narrow absorption components in the highly ionised species of SiIV and CIV. In the case of the WN6 star HD192163 each resonance transition in the above ions exhibits two components, one undisplaced in wavelength and one blueshifted. The latter components are shown to arise in the nebula NGC6888 surrounding HD192163, and these are the first observations of absorption lines arising in a nebula associated with an early-type star. The strengths of the 'interstellar' SiIV and CIV lines in four WR stars and two other early-type stars are compared. There seems to be no correlation in the strengths of these lines with either stellar distance or colour excess, suggesting that they arise not in the general interstellar medium but in material more intimately linked with the stars themselves.

ULTRAVIOLET observations by the Copernicus satellite of several early-type stars revealed sharp absorption lines in the resonance lines of highly ionised species of SiIV, NV and OVI (ref. 1). These lines have usually been attributed to the presence of a hot, low density coronal gas in the interstellar medium resulting from successive supernovae explosions and occupying much of interstellar space². Recent IUE observations of the X-ray binary source HD153919 (ref. 3) have shown the presence of sharp absorptions in SiIV and CIV, whose strengths are more consistent with the presence of an extensive region of photoionised gas associated with the X-ray source.

This article presents further observations of sharp 'interstellar' lines arising in highly ionised species. These are seen in the spectra of several WR stars which are being studied as part of an extensive investigation of this stellar class using the IUE satellite. The sharp absorptions in the SiIV, CIV and AlIII resonance lines of the star HD192163 are split into two

components, one undisplaced in wavelength and one blueshifted. The blueshifted components arise in the nebula NGC6888 surrounding the star, representing the first unambiguous observations of absorption lines in a nebula associated with a hot early-type star. The strengths of the observed sharp SiIV and CIV absorptions in four WR stars and two other early-type stars are compared. We conclude that there is no correlation between the strengths of these lines and either distance or colour excess, which suggests that their origin is not in the general interstellar medium but in material more intimately linked with the stars themselves.

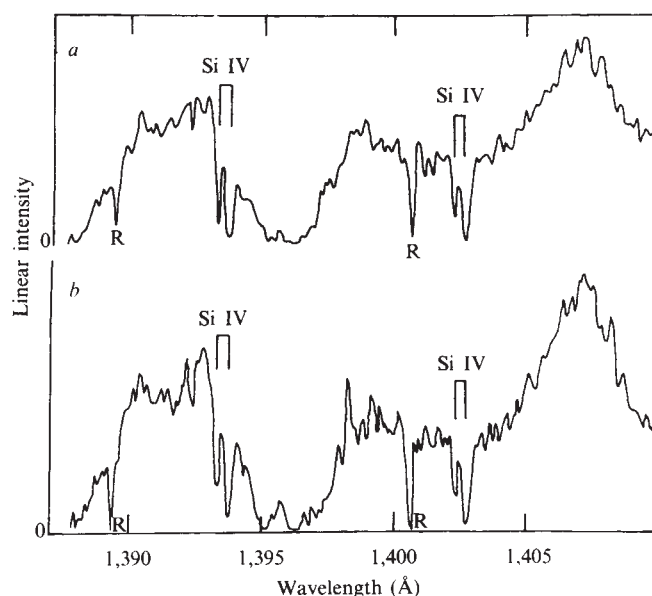


Fig. 1 The IUE spectra of HD192163 in the region of the SiIV 1,393.7 Å, 1,402.8 Å doublet. The two components to each SiIV line are marked. R marks the position of a camera reseau. *a*, SWP 1668; *b*, SWP 2517.

Table 1 IUE observations of four wolf-rayet stars

Star	Sp	V	$E(B-V)$	d (kpc)	IUE images*
50896	WN5	6.94	0.12	1.5	SWP 1335
192163	WN6	7.73	0.55	1.4	SWP 2517, SWP 1618, LWR 1580
156385	WC7	7.45	0.25	1.6	SWP 2519, LWR 2304
165763	WC5	8.25	0.21	2.5	SWP 2518, LWR 2303

*SWP, short-wavelength prime camera and image number; LWR, long-wavelength redundant camera and image number.

Observations

The IUE satellite has been described by Boggess *et al.*^{4,5}. The present observations of four WR stars were obtained in the high resolution mode ($\delta\lambda \sim 0.1-0.2$ Å) and cover the full available wavelength from 1,150 to 3,200 Å. Details of the observations and some information about the stars are given in Table 1. The

spectral types and V -magnitudes are taken from ref. 6; the colour excesses $E(B - V)$ from ref. 7 and the distances, d , from these data and the absolute magnitudes given in ref. 8.

Table 2 Equivalent widths, W_λ , velocity shifts, v , and column densities for the displaced SiIV, CIV and AlIII absorption lines observed in the UV spectrum of HD192163

Line	SWP 2517			SWP 1668		
	v (km s ⁻¹)	W_λ (Å)	log N	v (km s ⁻¹)	W_λ (Å)	Log N (cm ⁻²)
SiIV 1,393.7	86	0.21	13.36	97	0.17	13.27
SiIV 1,402.8	86	0.14	13.49	96	0.15	13.52
CIV 1,548.2	82	0.20	13.69	97	0.17	13.61
CIV 1,550.8	68	0.12	13.76	92	0.10	13.68
AlIII 1,854.7	93	0.15	12.96	97	0.12	12.86
AlIII 1,862.8	85	0.07	12.93	97	0.10	13.08

The raw data were reduced by the ESA observatory in Madrid and include corrections for relative intensities, background and echelle grating-blaze effects. The wavelength scales were determined by assigning the vacuum laboratory wavelengths to the narrow interstellar lines arising in low ionisation species (such as CII, 1,334.4 Å, 1,335.7 Å, OI 1,302.2 Å).

Sections of the two spectra of HD192163 covering the lines of SiIV 1,393.7 Å, 1,402.8 Å, CIV 1,548.2 Å, 1,550.8 Å and AlIII 1,854.7 Å, 1,862.8 Å are shown in Figs 1, 2 and 3 respectively. As well as the sharp components to these lines the SiIV and CIV lines are seen as broad P-Cygni profiles formed in the extended expanding atmosphere of the WR star. Each transition displays two sharp components; one, undisplaced at the rest frame of the other interstellar lines, and one, blueshifted. The velocities of the shifted components are given in Table 2 and are seen to be very similar, implying a common origin. The mean value is 90 ± 9 (r.m.s.) km s⁻¹.

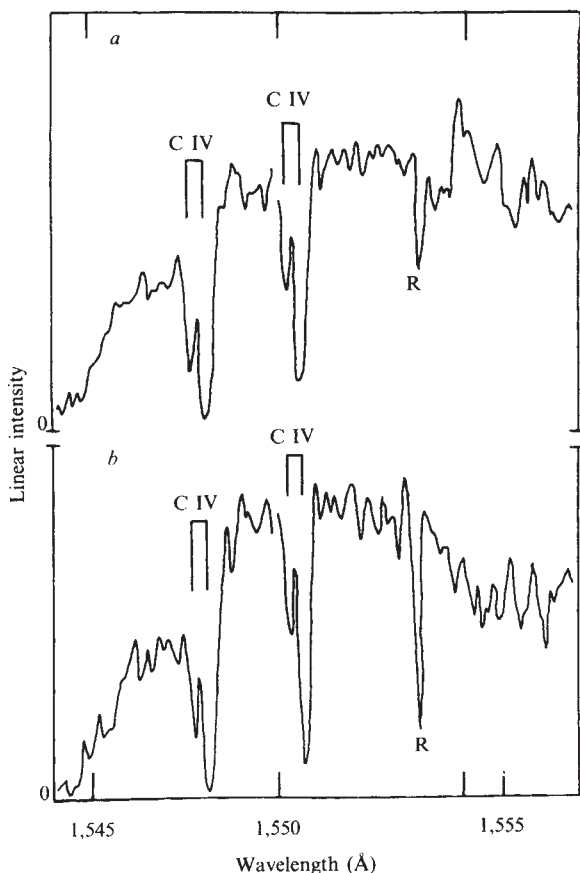


Fig. 2 The IUE spectra of HD192163 in the region of the CIV 1,548.2 Å, 1,550.8 Å doublet. The two components to each CIV line are marked. R marks the position of a camera reseau. *a*, SWP 1668; *b*, SWP 2517.

HD192163 is embedded in the nebula NGC6888, which is one of the ring nebula surrounding certain WN stars. Interferometric observations of this nebula in the visible H α , H β , and [NII] lines by Lozinskaya⁹ and Georglin and Monnet¹⁰ have demonstrated that the nebula is expanding from the central WR star with expansion velocities in the range 55–110 km s⁻¹. The infrared mean expansion velocity for NGC6888 is thus very similar to the observed velocity shifts of the sharp SiIV, CIV and AlIII displaced lines, demonstrating that these absorption components arise in NGC6888.

The NV 1,238.8 Å, 1,242.8 Å lines, however, are not seen in either displaced or undisplaced absorptions superimposed on the broad P-Cygni profiles of this doublet seen in the spectrum of HD192163. Their absence is discussed below. The 2,795.5 Å, 2,802.7 Å lines of the ion MgII are observed but are heavily saturated and broadened through normal interstellar absorption, thus masking any nebula component. Indeed the distance and reddening of HD192163 ensures that most of the other interstellar lines observed from common species are saturated, again masking any nebula components.

The measured equivalent widths and column densities for the nebula absorption components to the SiIV, CIV and AlIII doublets are given in Table 2; f -values for these transitions are from ref. 11. The column densities have been determined by assuming that these lines lie on the linear part of the curve of growth, an assumption confirmed by the fact that the doublet ratios for each ion are approximately in their expected ratio of 2:1. The strengths of the undisplaced components to these lines together with those observed in the spectra of other stars are given in Table 3.

Discussion

The electron density, N_e , and electron temperature, T_e , in the region of NGC6888 which gives rise to the observed optical emission have been determined as 400 cm⁻³ (ref. 12) and 19,000 K (ref. 9) respectively. The thickness of the nebula shell giving rise to the optical and radio emission has been determined as 0.01 pc (ref. 13). If it is assumed that the observed SiIV and CIV absorption arises in this region, the corresponding mean number densities of these species would be: $n(\text{CIV}) \sim 1.6 \times 10^{-3}$ cm⁻³ and $n(\text{SiIV}) \sim 8.3 \times 10^{-4}$ cm⁻³. Assuming that hydrogen is fully ionised in the nebula shell, $n(\text{H}) = N_e$, these numbers imply $n(\text{CIV})/n(\text{H}) \sim 4 \times 10^{-6}$ and $n(\text{SiIV})/n(\text{H}) \sim 2 \times 10^{-6}$. The further assumption of a normal cosmic abundance distribution in the nebula ($n(\text{C})/n(\text{H}) = 3.3 \times 10^{-4}$ and $n(\text{Si})/n(\text{H}) = 3.3 \times 10^{-5}$) would imply $n(\text{CIV})/n(\text{C}) \sim 10^{-2}$ and $n(\text{SiIV})/n(\text{Si}) \sim 0.06$. These values are completely at variance with the expected ionisation ratios for this region of the nebula. The ionisation balance calculations of Thuan¹⁴ for HII regions around OB stars indicate that with the effective temperature of the central WN6 star of 30,000 K (refs 7, 15) photoionisation is negligible for producing CIV and SiIV in the nebula, although this process could become significant if the stellar temperature were higher than 35,000 K. With $T_e = 19,000$ K and the ionisation balance calculations of Jordan¹⁶, Nussbaumer and Storey¹⁷ and Landini and Fossi¹⁸ the expected CIV/C and SiIV/Si ratios are both $\ll 10^{-4}$. Only by increasing the abundances of carbon and silicon in the nebula by over two orders of magnitude could the expected ionisation be accommodated by the observed SiIV and CIV column densities and the hydrogen density. Bearing in mind that the central star is a WN rather than a WC, this seems to rule out the optical and radio nebula region as the source of the SiIV and CIV absorption.

Johnson and Hogg¹³ have suggested that the nebula NGC6888 is formed by the sweeping up of the local interstellar material by the stellar wind of the central WR star, a hypothesis supported by Avedisova¹⁹ who showed that the mass of the nebula is consistent in this model with an original interstellar density of 1–2 atom cm⁻³. However, Wendker *et al.*²⁰ suggest that a substantial fraction of the nebula mass comes from the material shed by the WR progenitor during its evolution to the WR phase, a view supported by the recent evolutionary scenario

Table 3 Equivalent widths (Å) of undisplaced interstellar absorption lines in the ultraviolet spectra of four WR stars, ζ Oph and HD153919

Line	Star	HD192163 (SWP 2517)	HD192163 (SWP 1668)	HD50896	HD156385	HD165763	ζ Oph	HD153919
	$E(B-V)$	0.55	0.55	0.12	0.25	0.21	0.32	0.52
	d (kpc)	1.4	1.4	1.5	1.6	2.5	0.2	1.2
SiIV 1,393.7		0.32	0.29	0.24	—	—	0.02	—
SiIV 1,402.8		0.34	0.30	0.17	0.10	0.04	0.02	0.10
CIV 1,548.2		0.41	0.39	0.40	0.11	0.12	0.01	0.21
CIV 1,550.8		0.32	0.31	0.32	0.04	0.04	—	0.11
AlIII 1,854.7		0.18	0.19	0.11	0.16	0.12	0.06	—
AlIII 1,862.8		0.13	0.11	0.09	0.05	0.06	0.03	—
CII 1,334.5		0.60	0.70	0.28	0.30	0.50	0.22	—
CII 1,335.7		0.50	0.50	0.20	0.25	0.35	0.18	—
OI 1,302.2		0.60	0.45	0.24	0.40	0.36	0.20	—
SiII 1,526.7		0.50	0.55	0.13	0.24	0.45	0.16	—
SiII 1,304.4		0.50	0.40	0.16	0.17	0.30	0.13	—
SiII 1,260.4		0.70	0.75	0.25	0.60	0.60	0.22	—
SiII 1,259.5		0.34	0.40	0.20	0.30	0.28	0.15	—
SiII 1,253.8		0.37	0.30	0.18	0.22	0.30	0.11	—
SiII 1,250.6		0.26	0.30	0.20	0.18	0.25	0.10	—
MgII 2,802.7*		1.00	—	—	0.70	0.90	0.34	—
MgII 2,795.5*		1.20	—	—	0.80	0.90	0.31	—
MgI 2,852.1*		0.63	—	—	0.39	0.45	0.20	—

*The MgI, II lines in HD192163 measured from the LWR 1580 image.

of Conti²¹ and Willis and Wilson⁷ linking the Of and WR stars, and the very high mass loss rates ($\sim 10^{-4} M_{\odot} \text{yr}^{-1}$) that are now believed to be appropriate for the WR stars^{22,23}. In either case, as the velocities involved are large, considerable shock heating on the inner boundary of the nebula can be expected, with temperatures in this region perhaps lying in the range $3-6 \times 10^5$ K according to the model of Avedisova¹⁹. Therefore, the observed absorptions in the highly ionised SiIV and CIV species are probably formed in this hot region of the nebula. Note that

from the observed column densities of SiIV, CIV and AlIII and the ionisation balance calculations of Jordan¹⁶, Nussbaumer and Storey¹⁷ and Landini and Fossi¹⁸ for a low density plasma the infrared ionisation temperature is $\sim 60,000 \pm 8,000$ K, somewhat lower than predicted in the model of Avedisova¹⁹. If this temperature were correct, the expected NV/CIV ratio is $\sim 10^{-4}$ and thus the NV resonance line nebula absorptions would be expected to be negligible, in agreement with the present observations.

A comparison of the strengths of the undisplaced absorption components of AlIII, SiIV and CIV seen in the spectra of HD192163 with those observed in the three other WR stars listed in Table 1; in the 09V star ζ Oph^{24,25} and the X-ray binary source HD153919 (ref. 3) is given in Table 3. Also included in Table 3 are the measured strengths of the interstellar lines of the resonance lines of several common ions observed in these stars, the colour excesses $E(B-V)$ and the distances to these stars. The strengths of the low ionisation interstellar lines in HD192163 and ζ Oph are in the ratio $3(\pm 0.4):1$, which is broadly in line with the colour excess ratio of 2:1 bearing in mind the saturation effects which are present in most of these lines. However, the corresponding ratio for the high ionisation SiIV and CIV lines is ~ 20 , completely at variance with the colour excess and low ionisation gas column ratio. The corresponding ratio of the strengths of the SiIV and CIV lines in HD192163 and HD153919 is $\sim 3:1$, although in this case both the colour excesses and distances are very similar. There thus seems to be little correlation between the strengths of these sharp 'interstellar' lines of SiIV and CIV with either distance or colour excess.

Furthermore, a comparison of the strengths of these absorptions in the four WR stars currently observed in our IUE programme, confirms this assertion of a lack of a correlation with either distance or colour excess. Such a comparison for the CIV 1,548.2 Å, 1,550.8 Å doublet observed in the four WR stars listed in Table 1 is shown in Fig. 4. The most distant star, HD165763, exhibits the weakest CIV absorptions, whilst the least reddened star, HD50896, shows these lines with strengths comparable to those observed in HD192163. Although largely saturated the low ionisation interstellar lines listed in Table 3 have strengths in the four WR stars which are broadly in line with the relative stellar distances and colour excesses.

Conclusion

In the present sample of stars there seems to be no correlation between the strengths of sharp interstellar absorptions in the

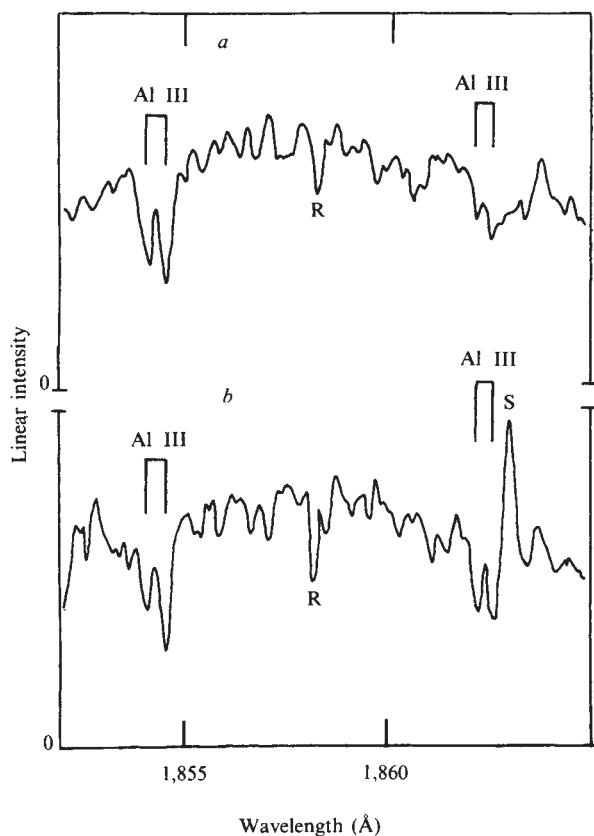


Fig. 3 The IUE spectra of HD192163 in the region of the AlIII 1,854.7 Å, 1,862.8 Å doublet. The two components to each AlIII line are marked. R marks the position of a camera reseau and S that of a noise spike in the data. a, SWP 1668; b, SWP 2517.

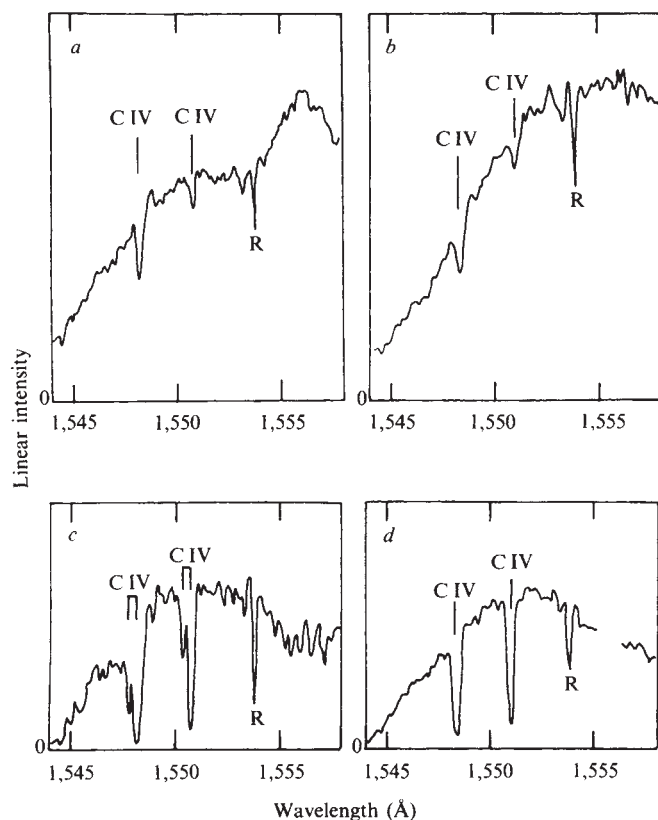


Fig. 4 The IUE spectra of the four WR stars: *a*, HD156385 (WC7); *b*, HD165763 (WC5); *c*, HD192163 (WN6); and *d*, HD50896 (WN5) in the region of the C IV 1,548.2 Å, 1,550.8 Å doublet. The sharp C IV interstellar components in each star are marked and, in the case of HD192163 the components that arise in the nebula NGC6888.

highly ionised species of Si IV and C IV with distance or colour excess which suggests that these features are not formed in the hot coronal gas permeating interstellar space. It seems more likely that their formation is a local effect closely linked to the WR stars themselves. A 'local' conclusion was also reached by Dupree *et al.*³ to explain the strengths of the highly ionised interstellar lines observed in the X-ray binary HD153919. They argue that the species are produced by photoionisation in the

radiation field of the X-ray source. In the present case it seems more profitable to consider the effects of the interaction of matter ejected by the WR stars and their progenitors with the interstellar medium.

Although there is no correlation between the strengths of the highly ionised interstellar lines in the four WR stars with other interstellar parameters, it is striking that they are much stronger in the two WN stars than in the two WC stars. The sample is too small to establish this as a real effect but the result may be linked to the different physical and chemical characteristics of the two WR sequences or their evolutionary state. Further observations of a larger sample of WR stars are clearly needed to establish this.

In the case of the WN6 star HD192163, it was shown above that absorption components in the Si IV, C IV and Al III resonance lines also arise in the nebula NGC6888 surrounding the star. More detailed modelling of these lines together with observations of the corresponding nebula emissions in these and other species, should enable the properties of that nebula to be accurately determined, a topic under investigation.

Finally HD192163 has been observed to have a pronounced excess strength in its 2,200 Å band which is believed²⁶ to arise in NGC6888. It may be pertinent to consider whether the great strength of the 2,200 Å band and of the C IV interstellar lines reported here (the strongest yet observed) are in some way linked.

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Short-range structure for amorphous intertransition metal alloys

Rong Wang

Pacific Northwest Laboratory, Richland, Washington 99352

Amorphous intertransition metal alloys may be a special class of the glassy state whose short-range structure is random tetrahedral close packing of soft atoms similar to those in the crystalline counterparts. A short-range structure is described based on random stacking of Kasper polyhedra and atomic disorder at the stacking misfit, and has tetrahedral sites, high atomic coordination numbers and asymmetric shapes of atoms.

A STRUCTURAL concept is introduced here for the amorphous intertransition metal alloys by alloying an early transition metal, T₁, with a late transition metal, T₂. These are shown in groups in Table 1. Recent investigation of formation, stability and properties of refractory amorphous alloys of W-Fe (ref. 1), Mo-Co (ref. 2), and Mo-Ni (ref. 3) at crystalline μ -phase or δ -phase compositions indicates that these amorphous alloys may have a crystal-like, short-range structure that deviates from the dense random packing of hard spheres (DRPHS)^{4–6}. Consequently, it has been suggested that the amorphous structure of a Mo₄₆Co₅₄ alloy is a random tetrahedral close packing of atoms resembling

Table 1 A division of transition metals of the Periodic Table

T ₁ element				T ₂ element			
Ti	V	Cr	Mn	Fe	Co	Ni	Cu
Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag
Hf	Ta	W	Re	Os	Ir	Pt	Au

the random interpenetration of Kasper polyhedra in three-dimensional space². This short-range structure for the intertransitional metal alloys is conceived from the concepts of Wang and Merz^{7,8} and Goodman⁹ that mixed atomic bondings of the crystalline counterparts are retained in the amorphous solids and contribute to their thermal stability. We present here evidence and structural features supporting the argument that short-range structure in this type of metallic glass should closely resemble that found in compositionally related crystalline phases.

Evidence for crystal-like short-range structure

Amorphous intertransition metal alloys probably have a crystal-like, short-range structure because of the following unique aspects of formation, structure and properties, which are closely related to those of the intermetallic compounds.

(1) Formation of the amorphous intertransition metal alloys is favoured by compositions that are at, or near, a eutectic point or a complex-structured intermetallic compound. Formation by quenching from the liquid state clearly benefits from an under-cooled liquid with composition near the eutectic point, while at high cooling rates (that is by vapour deposition) formation occurs at compositions of the intermetallic composition^{1-3,10}.

(2) Amorphous intertransition metal alloys generally show a sharp first diffraction peak that corresponds to a coherent diffracting domain size between 13 and 18 Å, depending on the method of preparation, composition and cooling rate^{1,2,11,12}. The sharp diffraction peak indicates a high degree of short-range order which was once considered as evidence of microcrystallinity for liquid-quenched Nb-Ni and Ta-Ni alloys¹². The calculated scattering intensities based on relaxed DRPHS models only qualitatively explain the details of the observed intensities for amorphous Cu-Zr alloys¹³⁻¹⁵. The discrepancy between the observed and calculated scattering intensities also was found in amorphous Nb₃Ge and Nb₃Si¹⁶, due to the asymmetrical nearest-neighbour maximum found in measured dis-

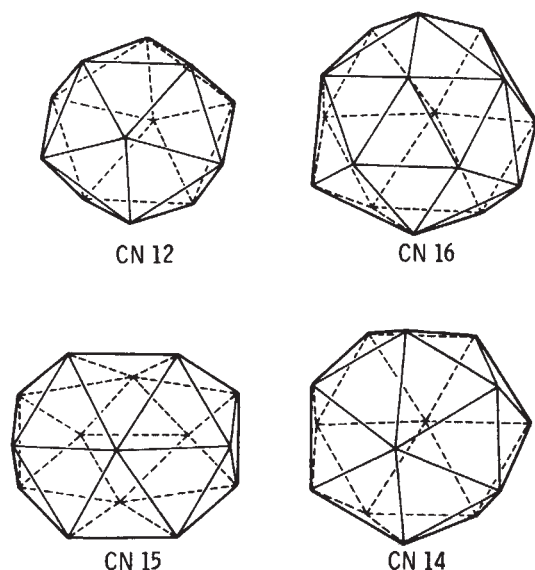


Fig. 1 The four triangulated coordination polyhedra with 5- and 6-fold vertices observed in the intertransition metal compounds (from ref. 27).

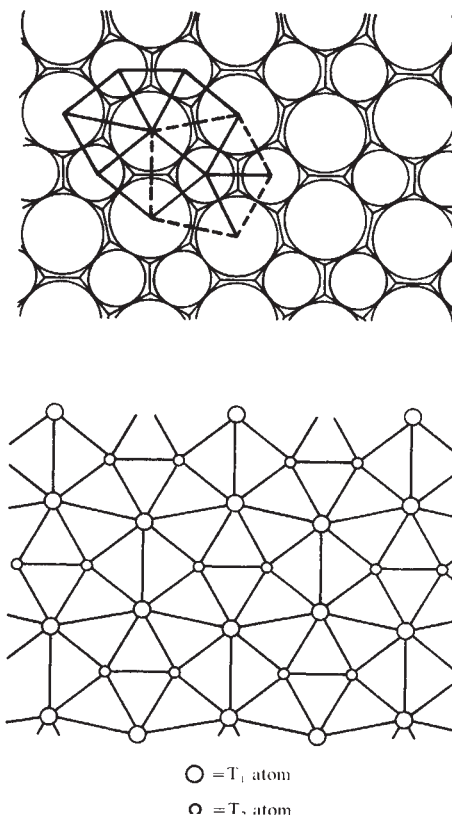


Fig. 2 Two-dimensional analogue of Kasper polyhedra to show irregular triangles that will be irregular tetrahedra in three-dimensional space (from ref. 26).

tribution functions for amorphous Nb₃Ge. Thus, local order in amorphous Cu-Zr has been considered as being related to the crystallised phases¹⁷.

(3) The densities, or packing factors, calculated from the DRPHS models were between 10 and 30% smaller than those observed for the amorphous alloys, depending on the relaxation processes^{16,18,19}. The measured densities of the amorphous intertransition metal alloys are closer to the values of the corresponding crystalline intermetallic compounds^{1,2}.

(4) High thermal stability is usually associated with the amorphous intertransition metal alloys¹⁰; that is, the crystallisation temperatures of Nb₄₀Ni₆₀, Mo₅₀Ni₅₀, and Zr₅₀Cu₅₀ are above 600 °C and those of W₅₀Fe₅₀, and Mo₄₆Co₅₄ alloys are above 800 °C^{1,2}. Several amorphous films of Ta-Re, Mo-Re and Mo-Ru²⁰ at the compositions near the crystalline intermetallic compounds also exhibit similar high thermal stabilities. On the other hand, thin films of single transition metals, such as Zr, Hf, Ta, Mo, Cr, W, and Re, are either microcrystalline or amorphous but stable only below room temperature^{20,21}.

(5) High microhardnesses ranging from 800 to 1,100 kg mm⁻² are typical for the amorphous intertransition metal alloys, even though the differences in electronegativity between the two alloying elements are small. The microhardnesses are comparable to those of the crystalline intermetallic compounds and indicate strong covalent bondings involving d electrons; these bondings also resemble those of the crystalline phases.

These properties suggest that amorphous intertransition metal alloys belong to a special class of glassy state that involves strong atomic interactions among d electrons—similar to those in the intermetallic compounds. Thus, the short-range structure is expected to incline more towards the short-range order of the crystalline phase and to deviate from the random close packing of hard sphere models as far as the metallic glasses and the simple liquids are concerned.

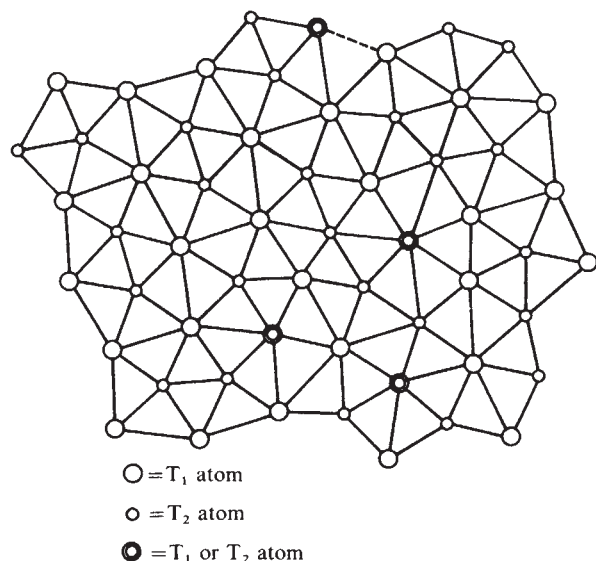


Fig. 3 Proposed structure for amorphous intertransition metal alloys as made by random stacking of irregular tetrahedra shown in a two-dimensional analogue.

Short-range structure

The short-range structure of the amorphous intertransition metal alloys is proposed to be random tetrahedral close packing of soft atoms. This structure is derived from the crystal chemistry of the intertransition metal compounds: the crystal structures are primarily based on tetrahedral close packing of atoms²²⁻²⁵. One can achieve packing with a single type of tetrahedral interstices only by irregularly shaped tetrahedra. Intensive analyses of the known structures of intertransition metal compounds have revealed that there are only four triangulated coordination polyhedra (the so-called Kasper polyhedra²²) that have 5- and 6-fold vertices as shown in Fig. 1. In many crystal structures, these polyhedra interpenetrate in such a way that every vertex atom becomes the centre of a polyhedron. Figure 2 shows the meshing of polyhedra (the 5-fold vertices, for instance). It is taken from Laves' analog²⁶ and is viewed in two-dimensional space. In this structural analogue, the T_1 atom has a CN 7 (seven neighbours close to each T_1 atom), and the T_2

atom has a CN 5 (five neighbours close to each T_2 atom). Crystal structures based on the stacking of these Kasper polyhedra for intermetallic compounds are discussed in detail by Kasper²², Shoemaker *et al.*^{24,25} and Bergman *et al.*²⁷.

Consequently, the proposed short-range structures of the amorphous intertransition metal alloys will also contain interpenetrated Kasper polyhedra similar to those occurring in the intermetallic compounds. The short-range structure of amorphous alloys may be constructed by random stacking of all four types of the Kasper polyhedra, and by introducing atomic disorder at the stacking misfit. A two-dimensional analogue can be used to show the structure of amorphous alloys (Fig. 3) and to compare it with that of the crystalline form (Fig. 2).

The amorphous structure was composed of two sets of stacking configurations based on the 5-fold vertices—the stacking configuration for the crystalline structure (Fig. 4) and the additional stackings uncommon to the crystalline structure (Fig. 5).

Due to long-range order, the stacking configurations for the crystalline structure are limited by three ways able to connect two vertices and one way able to stack four vertices (Fig. 4). However, the amorphous structure contains additional random stackings, as in Fig. 5, which shows both perfect matching of the vertices side by side and the stacking misfit where stacking cannot be matched at one atomic site.

Stacking misfit causes atomic disorder, that is ambiguity of atomic identity at the corner of the 5-fold vertex. For example, the atomic disorder at site 1 occurs because both T_1 and T_2 atoms should occupy this site if the edges of the vertex are made of four T_1 and one T_2 atom. This atomic disorder is common when more than two vertices are stacked randomly. The atomic disorder at site 2 is caused by stacking of three vertices in a specific configuration so that T_1 atoms form a triangle in which one side (connected by dash line) is too short for the normal T_1 - T_1 distance. Either this compresses the T_1 atoms, or one of the T_1 atoms will be replaced by a T_2 atom. In fact, these stacking misfits are also observed in intermetallic compounds at atomic coordination points 13 and 14 (ref. 28).

In constructing the amorphous structure analogue, many 5-fold vertices need to be distorted slightly from ideal shapes in the crystalline structure to lower the stacking misfits in the amorphous structural framework. These distortions were made by hand-adjusting the atomic positions in the vertices after the framework was completed. The atomic position adjustments would not usually exceed 10% of its interatomic distances. The distortion causes the final amorphous structure analogue, shown in Fig. 3, to contain a range of interatomic distances as shown in Fig. 6. As far as short-range atomic interaction is concerned, the two-dimensional amorphous structure analogue is similar to that of the crystalline structure, except a small portion of T_1 and T_2 atoms have the intermediate CN 6.

Discussion of the short-range structure

The structure described here is truly amorphous and contains continuous, random packing of atoms. It should not be considered as a microcrystalline model because there are no apparent line or surface discontinuities such as grain boundaries, and there is no periodicity in any direction. However, short-range atomic interactions, similar to those of crystalline compounds, are retained by stacking various types of polyhedra and atomic disorders at random. The types of polyhedra and the stacking configuration that dominate the amorphous structure would vary according to the composition, alloy system and cooling rate; primarily, however, they would be those of the nearby crystalline compounds, such as the μ -phase polyhedra²⁸ for amorphous $W_{50}Fe_{50}$, $Mo_{46}Co_{54}$, and $Nb_{50}Ni_{50}$.

Several features related to atomic size, coordination number and atomic interactions can be expected for the real amorphous intertransition metal alloys. The atomic size in these amorphous structures will be less specific because the atoms will assume more asymmetric shapes as the atomic coordination number increases from 12 to 16 (those observed in the intermetallic compounds). Consequently, high packing density and atomic

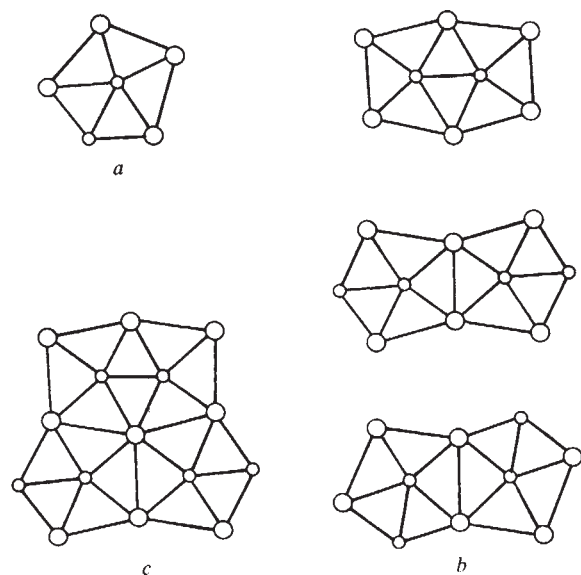


Fig. 4 Stacking configurations of the 5-fold vertices in both crystalline and amorphous structure analogs: a, a single 5-fold vertex; b, connections of two vertices; and c, stacking of four vertices.

interactions among unlike atoms are expected. These can be viewed from the two-dimensional structure analogue of Fig. 3 which consists of 29 T_1 atoms, 25 T_2 atoms and four disordered atoms. A packing density similar to that of the crystalline analogue is expected because T_1 atoms have CN 7 and CN 6, but T_2 atoms have CN 5 and CN 6, and small percentage (7%) of the disordered atoms. The occurrence of different atomic interactions (Fig. 6) shows that with a nearly 1:1 ratio of T_1 and T_2 atoms, there are almost twice as many T_1 - T_2 interactions than T_1 - T_1 interactions, and the T_2 - T_2 interactions are less significant. Diffraction studies have indicated that such strong atomic interactions occur among the unlike atoms for the real amorphous structures, such as Cu-Zr¹⁵, Nb₃Ge¹⁶, and RE-Tm^{18,19}.

Relationship to the formation and thermal stability

The formation and thermal stability of the short-range structure that contains a mixture of all four types of Kasper polyhedra can be understood as follows. The polyhedra represent possible low-energy configurations for atoms to be bonded in the solid, in positions that are separated by small energy differences. During quenching from the liquid or vapour state, the availability of four types of polyhedra allows several alternatives, or saddle-point energies, for atoms to be bonded to their neighbouring atoms in a way that prevents long-range atomic rearrangement. The total energy will not be significantly influenced by those small energy differences as long as the atoms are locally satisfying the requirement for strong d-d electron interactions. This explains the formation and stability of the amorphous inter-transition metal alloys.

For this type of amorphous structure, resembling a short-range ordered version of the crystalline phases, those factors governing the stability of the intermetallic compounds, such as the electron-to-atom ratio (e/a), the electronegativity, and the atomic size difference, would also be important for the forma-

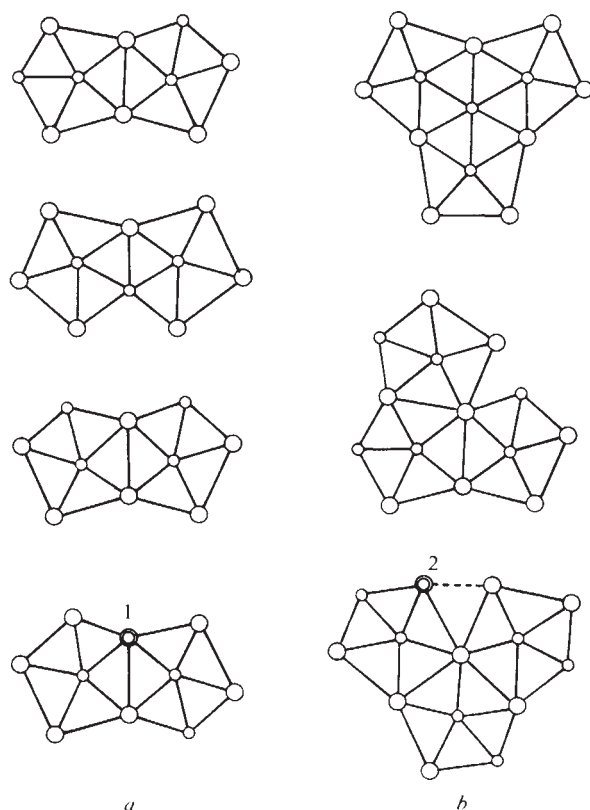


Fig. 5 Additional stackings of the 5-fold vertices with and without stacking misfits in amorphous structure analogue *a*, connections of two vertices; and *b*, stackings of three vertices.

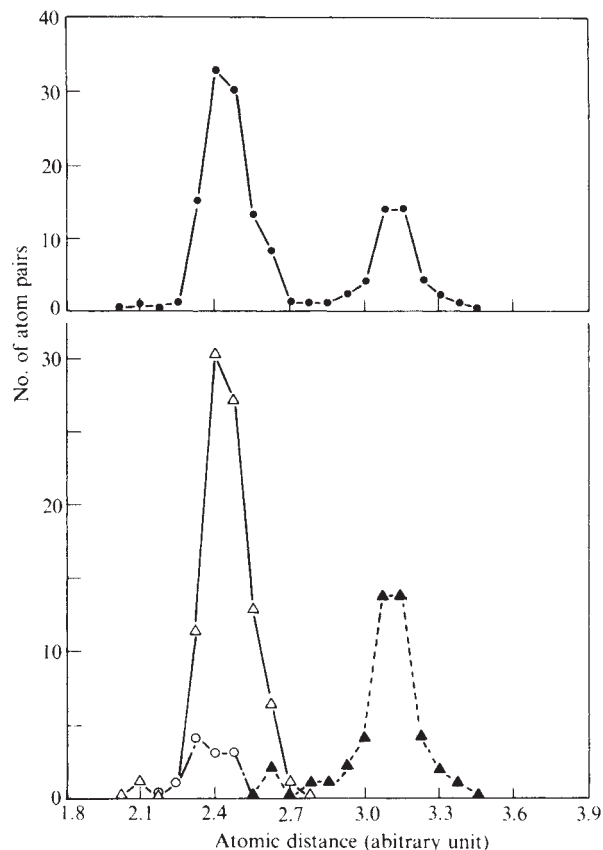


Fig. 6 Number of atom pairs and their distances on an arbitrary scale for the two-dimensional amorphous structure analogue of Fig. 3. $\triangle$ - $\triangle$, T_1 - T_2 ; $\blacktriangle$ - $\blacktriangle$, T_1 - T_1 ; $\circ$ - $\circ$, T_2 - T_2 ; $\bullet$, summation of atom pairs.

tion and the stability of the amorphous structure¹⁰. In this regard, the short-range structure will apply to all the amorphous intertransition metal alloys whose crystalline counterparts follow the crystal chemistry principles as electron compounds. It is expected that binary and ternary amorphous alloys will be formed in the composition ranges in which intermediate phases such as σ , μ , δ , P and R phases are present. The above formation criteria and short-range structures can probably be extended to the other amorphous alloys based on Cr₃Si (A15), Laves (C14, C15, and C36) and CaCu₅ (D2_d) type phases that are related to the σ phase.

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Evidence of a new isotopic anomaly from titanium isotopic ratios in meteoric materials

H. R. Heydegger*†‡, J. J. Foster* & W. Compston*

* Research School of Earth Sciences, Australian National University, Canberra, ACT, Australia 2600

† Department of Chemistry, Purdue University, Calumet Campus, Hammond, Indiana, 46323

‡ Enrico Fermi Institute, The University of Chicago, Chicago, Illinois, 60637

Titanium isotopic ratios in some terrestrial and meteoritic materials have been measured. Most have the same ratios within the experimental precisions. Some inclusion materials from the Allende meteorite have a statistically significant enhancement of the order of 1‰ in the 50/49 ratio, probably due to a nucleogenic anomaly in ⁵⁰Ti abundance.

SIGNIFICANT variations in the isotopic ratios of certain elements in some meteorites have been well established^{1–11}. Recent results^{10–13} show that some meteoritic materials may be simultaneously 'anomalous' in several elements. Numerous mechanisms^{14–18} have been proposed to explain these observations, and a common engendering phenomenon will probably be found for most, if not all, of the anomalies. To make a correct hypothesis, however, we need to establish the nature and magnitude of the anomalies in a large variety of elements.

A study of the isotopic composition of titanium in terrestrial and meteoritic materials, and especially inclusions in the carbonaceous chondrite Allende, has been undertaken, and some general results are reported here.

Titanium was studied because: (1) the titanium isotopic abundances observed in most materials are thought to be due to a combination of nucleosynthetic mechanisms¹⁹. Therefore it seems unlikely that the same pattern would arise from the phenomenon(a) which caused the anomalies in other elements; (2) most isotopic anomalies have been reported from refractory phases, and titanium is a refractory element in the classical condensation sequence²⁰; (3) carbonaceous chondrites are thought to have undergone less chemical and physical processing since their original formation, and inclusions in Allende have been the prime source of anomaly-bearing materials; (4) although no evidence of titanium isotope anomalies has been presented previously, uncertainties on the only reported study²¹ of similar materials were at a level sufficiently high ($\sim \pm 0.3\%$) for many anomalies observed in other elements to have been obscured.

Experimental techniques

Samples were chemically processed using standard dissolution and cation exchange methods^{22,23}. Blanks ran about 50 ng TiO₂. Samples containing about 50 µg titanium were loaded onto triple rhenium filaments as aqueous or HF slurries, and were run on a mass spectrometer as described elsewhere²⁴. High side-

filament currents (about 3 A) were required to obtain sufficiently large ion currents ($\sim 10^{-13}$ A) for the less abundant isotopes. All data were taken using Ti⁺ beams, alternating between 47/49 and A/49, where A was 46, 48, or 50. A 'group' consisted of at least four 12 ratio sets for 47/49 and one set each for 46/49, 48/49, and 50/49, a minimum of six groups being obtained in the measurement of most samples. The amplifier zero level was measured at mass 52.5 twice during each group.

For all samples, the observed isotope ratios were found to change with time in a manner consistent with the Rayleigh single stage mass fractionation model, and to an extent comparable with that displayed by other refractory elements (such as Mg) (ref. 13).

To facilitate comparisons, all observed ratios were normalised to the value 1.3360 for 47/49, which is the weighted mean of the observed values obtained for the terrestrial materials and is assumed to be accurate to within $\pm 1\%$ of the true value. The ratio 47/49 was chosen as the basis for normalisation because there are no stable nuclidic isobars at these mass numbers, as there are for the other Ti isotopes. Observed ratios were automatically corrected for contamination from non-Ti nuclidic isobar ions as follows: masses 46 and 48 for Ca using mass 40; mass 50 for V using mass 51 and for Cr using mass 52. Data were not accepted if the isobaric contamination exceeded 0.1%. The entire mass spectrum between 38 and 56 was routinely recorded before the first group and after the last group for a given sample; a record between masses 45 and 53 was taken between groups. No data were accepted if base line irregularity greater than normal electronic noise levels between titanium mass numbers or unusual peak shapes were observed. In a few cases, it was necessary to correct for zero level drift (assumed to be linear with time) during a set. A few ($\sim 2\%$, mostly 48/49, which is more sensitive to transient baseline changes) outlying ratios and set means were rejected by Chauvenet's criterion in computing the means. In Tables 1–4, the uncertainties quoted are three times the sigma of the mean estimated from the observed dispersions of individual results. The three sigma level is preferable here to the more common two sigma level because, on average, one of every 20 replicate means at the latter level, but only one of every 250 replicate means at the former level, will be further from the grand mean than the quoted uncertainty.

Terrestrial materials

Titanium was isolated from the terrestrial materials listed in Table 1. More than 1,000 individual ratio measurements were made for each A/49 on samples prepared from these terrestrial

Table 1 Comparison of terrestrial materials

Material*		Normalised† Ti isotope ratios $\pm 3s(\bar{x})\ddagger$		
		46/49	48/49	50/49
Ti metal	$\bar{x}_w$	1.4618 $\pm$ 0.0014	13.442 $\pm$ 0.004	0.9723 $\pm$ 0.0008
	$\bar{x}_u$	1.4622 $\pm$ 0.0025	13.443 $\pm$ 0.006	0.9726 $\pm$ 0.0010
NBS TiO ₂	$\bar{x}_w$	1.4614 $\pm$ 0.0008	13.441 $\pm$ 0.008	0.9730 $\pm$ 0.0002
	$\bar{x}_u$	1.4612 $\pm$ 0.0009	13.445 $\pm$ 0.012	0.9730 $\pm$ 0.0003
Potassium titanate	$\bar{x}_w$	1.4616 $\pm$ 0.0008	13.442 $\pm$ 0.005	0.9728 $\pm$ 0.0005
	$\bar{x}_u$	1.4613 $\pm$ 0.0010	13.445 $\pm$ 0.006	0.9728 $\pm$ 0.0006
Rutile	$\bar{x}_w$	1.4614 $\pm$ 0.0009	13.443 $\pm$ 0.009	0.9723 $\pm$ 0.0006
	$\bar{x}_u$	1.4613 $\pm$ 0.0010	13.442 $\pm$ 0.010	0.9722 $\pm$ 0.0005

* Ti metal: Batch Ti/002, 99.9% Roc-ric Co. NBS TiO₂: SRM 154, US NBS. Potassium titanate: BDH Analar grade, 99.93%. Rutile: Beachsand concentrate from south Queensland, supplied by the Bureau of Mineral Resources, Canberra. $\bar{x}_w$, weighted (by inverse variance) mean. $\bar{x}_u$, unweighted mean.

† Normalised to (47/49) = 1.3360.

‡ s_x Estimated standard deviation of mean based on observed dispersion.

materials. Normalised results for measurements made in the period during which those on the meteoritic materials were also made are presented in Table 1 for both weighted (by inverse variance) and unweighted means, along with the three sigma of the mean uncertainty estimates. No significant differences were found between these recent means and those based on a comparable number of earlier measurements of the same (and other terrestrial) materials.

Because no significant differences among the various terrestrial materials are evident within the precision of the current measurements, all of this terrestrial titanium was assumed to be identical in its isotopic composition regardless of source, and the results were combined through weighted individual sample (six set) means, with results presented in Table 2 as terrestrial. The typical relative uncertainty of the means ($3\sigma_x/\bar{x} \sim 0.03\%$) is comparable to that reported recently by other laboratories for isotopic ratios of other elements in similar materials^{10,13}. Our values agree with most of the reported isotopic analyses of titanium well within the estimated $\pm 1\%$ accuracy. Therefore, our method apparently gives reasonable accuracy and precision for terrestrial materials.

Meteoritic materials

Allende whole rock powder: several samples were prepared directly from Allende powder (TiO₂ content 0.15%) obtained from the US National Museum (3529, S19, P20). The combined (weighted) normalised individual sample mean results of these measurements are given in Table 2.

The Allende whole rock powder titanium isotopic ratio results are not distinguishable from those for terrestrial materials within the experimental precision, which is comparable to that obtained for terrestrial materials. Therefore, our analytical methods seem to apply to Allende as well as to terrestrial materials.

Allende whole rock powder chemical leach fractions: Anders *et al.*^{25,26} have reported that most of the anomalous rare gases are associated with a small amount of the material in Allende, which they concentrated through a sequence of chemical leaches of Allende powder. From its chemical properties, they deduced this carrier to be a sulphide-rich phase. It has been proposed²⁷ that such a phase might be rich in ⁴⁶Ti sulphide derived from a condensing supernova shell. Therefore, a sequence of leaches similar (see Table 2 for details) to that used for the rare gas work^{25,26} was performed on two separate (~ 0.5 g) samples of the Allende powder described above. The titanium isotopic ratios of these various separate acid leach (two HCl, one HF, two HNO₃) samples were found to be the same within experimental precision, and all results were, therefore, combined (as six set means) to produce the values in Table 2. The overall relative precision is again roughly comparable with that observed for terrestrial materials. Included in these means are data from three samples which had been chemically reprocessed for titanium after the usual chemical treatment. The data for the reprocessed samples seemed to disperse in the same manner about common means as those for the one chemical cycle samples.

Table 2 Mean results for terrestrial and Allende materials

Material*	Normalised† Ti isotope ratios $\pm 3s(\bar{x})\ddagger$			Mean no. of measured ratios included
	46/49	48/49	50/49	
Terrestrial	1.4613 $\pm$ 0.0005	13.441 $\pm$ 0.002	0.9728 $\pm$ 0.0005	359
Allende powder whole rock	1.4614 $\pm$ 0.0007	13.439 $\pm$ 0.004	0.9728 $\pm$ 0.0002	245
Acid leaches‡	1.4611 $\pm$ 0.0004	13.439 $\pm$ 0.007	0.9733 $\pm$ 0.0002	367
Residue‡	1.4613 $\pm$ 0.0010	13.441 $\pm$ 0.005	0.9725 $\pm$ 0.0014	51
Pyroxene	1.4614 $\pm$ 0.0002	13.444 $\pm$ 0.005	0.9737 $\pm$ 0.0007	110
Mean inclusion whole rock	1.4620 $\pm$ 0.0013	13.439 $\pm$ 0.006	0.9733 $\pm$ 0.0004	462
Inclusions with oxygen anomalies	1.4619 $\pm$ 0.0002	13.440 $\pm$ 0.013	0.9738 $\pm$ 0.0003	158

* See Table 1 and text for description of materials.

† See Table 1 for details.

‡ Separate contacts with concentrated HCl, HF, and HNO₃, each for ~ 12 h at about 80°C. Cycle performed twice with each Allende whole rock powder sample, with like fractions from both cycles combined and treated for Ti in usual manner. Acid leaches represents the combined data from two HCl, one HF, and two HNO₃ soluble fractions. Residue represents Ti isolated in the usual manner from the insoluble residue of the above acid leaches.

Allende inclusions: the largest oxygen and magnesium anomalies have been found in inclusions in Allende. Therefore, titanium from a variety of Allende inclusions has also been measured in this work. Most of these samples have been well documented mineralogically and chemically²⁸. We obtained aliquots of powdered whole inclusions which had not been (and were not) further separated before chemical processing. The samples varied between about 0.5 and 2.5% in TiO₂ content and represented all classes of inclusions listed by Taylor and Mason²⁸. These materials were processed using the same chemical procedures as for the terrestrial and whole rock materials described above; however, in some cases, the order of the ion-exchange steps was changed. Due to the small amounts of material available, replicate samples of all materials could not be processed; however, in those cases where replication was possible, agreement was found to be consistent within the precision of the individual measurements involved. The frequency distributions for the measured isotopic ratios of terrestrial and of inclusion material overlap sufficiently that, in the absence of several replicate determinations, none of the individual inclusions can be convincingly demonstrated to be different from terrestrial material in titanium isotopic composition. However, as the results for the various samples seem to be dispersed no more widely than true replicates would be, all data on whole rock inclusions were arbitrarily combined (weighted) as six set means to obtain a single 'mean inclusion' value for each ratio. These results are also shown in Table 2.

Mineral separates from Allende inclusions: mineral separates are the most fertile ground for isotopic anomalies for several elements. A pyroxene separate from an Allende inclusion (USNM3529, 32 described in ref. 29) was run in duplicate samples in the usual manner. The mean results are shown in Table 2. Uncertainties quoted are based on the observed dispersion of these true replicates and are similar to the others quoted.

Allende material with oxygen anomalies: some inclusion whole rock and density separates from Allende in which oxygen anomalies had been found were processed for titanium in the usual manner. As three of the samples (all mostly pyroxene from Al 6S3 and Al 3S4) have virtually identical oxygen anomalies³⁰ and because each of the individual samples seems to be anomalous in titanium (see Table 3) and because the normalised individual sample mean data points fall within the area inferred to exist for replicate results, the results for these samples, including one chemically reprocessed sample, have been combined to provide the mean values shown in Table 2. As usual, the quoted uncertainties are computed from the dispersion of the individual sample values.

Discussion

The data represented by the values shown in Table 2 have been carefully considered and, in particular, all apparent deviations from the terrestrial values have been tested for significance using the *t*-test. If 47/49 is assumed to be the same in all materials measured, the results of this study of titanium isotope ratios show that, within the limits of the relevant experimental precisions: (1) terrestrial materials from four different sources

display the same values with a mean relative three sigma of the mean uncertainty of about 0.03%; (2) Allende whole rock is not distinguishable from mean terrestrial material; (3) the chemical leaches from Allende whole rock, while showing some variations, do not differ significantly (three sigma level) from mean terrestrial material in their means; (4) results on inclusions and on a mineral separate extracted from an inclusion scatter in a manner consistent with the precision observed for the replication of other materials and with mean values within 0.1% of (and not different from at the three sigma level) the mean terrestrial values for all ratios. However, note that arbitrary combination of all inclusion values would tend to dilute the effect of any anomalous material which might be present in only one or some of the inclusions or fractions thereof. Therefore, (5) if only inclusion material with documented oxygen anomalies is considered, the frequency distribution of individual 50/49 set means is found to be displaced from that for terrestrial materials, as shown in Table 4, and the mean 50/49 is found to be significantly (greater than three sigma of the mean) higher than for the mean terrestrial material. The observed *t* is 3.95, which for eight degrees of freedom represents about four chances in 1,000 that both the terrestrial and oxygen-anomalous sample means represent individual results drawn from a single normal frequency distribution. This is highly unlikely and we conclude that these meteoritic materials are different from terrestrial materials in their titanium isotopic composition to an extent comparable with recently reported anomalies in other elements in Allende^{8,11}.

Although the statistical analyses described above confirm a significant difference between the isotopic ratios in question, they cannot be used to exclude the presence of any of several possible systematic errors which might cause such a difference. We have carefully considered all such possibilities. For example, the origin of this observed enhancement of the 50/49 ratio in these inclusions cannot be single-stage Rayleigh mass fractionation because the process of normalisation would, of course, eliminate or at least obscure any pre-laboratory physicochemical mass fractionation such as has been observed for other elements, as well as that introduced by the mass-spectrometric measurement procedures. However, any normalisation can also distort the nature and extent of any nucleogenic anomalies present. The effects of such alternate normalisations have been extensively investigated and found to provide results consistent with expectations as to their nature and magnitude but of poorer precision due to the additional extrapolations and interpolations required vis-a-vis the 47/49 normalisation. Therefore, in the absence of evidence to the contrary, we prefer to use the latter.

Thus, either a depletion of ⁴⁹Ti or an enhancement in ⁵⁰Ti abundance is required. Ockham's Razor can be applied to argue against the former in that simultaneous appropriate depletions in the other three titanium isotope abundances would be required to maintain the agreement with terrestrial values obtained for the other ratios. Therefore, an enhancement at mass 50 is indicated. As described above, mass scans allowed the rejection of data where questionable peak shapes or baselines were present and corrections for known nuclidic isobars present during each set were made, with no systematic trends evident.

Table 3 Magnitudes of isotopic ratio anomalies

Allende inclusion*	Relative magnitudes (p.p.t.) of anomaly in isotopic ratio					⁵⁰ Ti/ ⁴⁹ Ti§
	¹⁷ O/ ¹⁶ O*	¹⁸ O/ ¹⁶ O*	²⁶ Mg/ ²⁴ Mg†	²⁹ Si/ ²⁸ Si‡	³⁰ Si/ ²⁸ Si‡	
Al 3S4	-39.3	-38.0	0.3 to 135	-0.3	1.8	1.2 ± 0.9
Al 6S3	-38.8	-36.6	—	—	—	1.2 ± 0.9
						2.0 ± 1.2
						Average = 1.4 ± 0.7

* Ref. 30. † Ref. 35. ‡ Ref. 36.

§ Values are individual sample means and mean (weighted) of combined results for both samples. Uncertainties quoted are three sigma of the mean estimated from dispersion (see text).

|| Chemically reprocessed.

Table 4 Frequency distributions of $^{50}\text{Ti}/^{49}\text{Ti}$ set means

Material*	Relative no. of normalised† individual set means with 50/49 value						
	<0.9716	0.9716–24	0.9724–32	0.9732–40	0.9740–48	0.9748–56	>0.9756
Terrestrial	0.03	0.26	0.42	0.29	0	0	0
Inclusions with O-anomalies	0	0.05	0.23	0.32	0.23	0.14	0.05

* See Table 1 and text for descriptions of materials.

† Normalised to $(47/49) = 1.3360$.

Therefore, in the absence of any evidence of unusual conditions during the measurement of any of the three anomalous samples, we conclude that the ^{50}Ti abundance is higher than normal in these oxygen anomaly-bearing inclusions.

The coincidence of anomalies in different elements in the same material suggests a common origin in a nucleosynthetic history for some fraction of the material that is distinct from the history for most of the materials studied. In attempting to account for the normal nuclide abundance pattern, various workers have modelled both hydrostatic and explosive thermonuclear processes. Despite great uncertainties in both the nuclear physical and the astrophysical input information, considerable success has been achieved. Such calculations^{31–33} indicate that explosive carbon burning can result in matter which is simultaneously enriched in ^{16}O , ^{26}Mg , and ^{50}Ti , just the coincidences reported in this work and previously^{30,35}, as shown in Table 3.

The picture concerning the magnitude and variety of isotopic anomalies is far from complete³⁷. Therefore, it seems that

additional studies of the correlation of anomalies in different elements must be undertaken. In particular, in the case of titanium, the existence and locus of a true anomaly (rather than a highly improbable statistical fluctuation or an undetected systematic error) must be independently confirmed, and the anomaly-carrying phase(s) must be identified. These are tasks for which the high resolution ion microprobe may be particularly well suited.

In conclusion, the results of this study indicate that a nucleogenic anomaly in titanium, most probably an enrichment in ^{50}Ti abundance, exists in some oxygen-anomaly bearing Allende inclusions.

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Volcanic eruption through a geothermal borehole at Námafjall, Iceland

Gudrún Larsen & Karl Grönvold

Nordic Volcanological Institute, University of Iceland

Sigurdur Thorarinsson

Science Institute, University of Iceland, Reykjavik, Iceland

During the present rifting episode in the Krafla fault swarm in North Iceland, large scale horizontal movement of basaltic magma is taking place underground. On 8 September 1977 magma reached the depth range of boreholes in the Námafjall geothermal field. In 20 min 3 ton of magma erupted through an 1,138 m borehole forming a small scoria sheet.

THE eruption on 8 September 1977 in the Námafjall geothermal field was a part of a rifting event that took place during that day, and which itself is a part of a major rifting episode which has been in progress on the Krafla fault swarm in North Iceland since 20 December 1975^{1–4}. The eruption through the borehole provides further evidence for a large scale magma movement along the fault swarm initially postulated from ground deformation observations¹.

The Krafla fault swarm is ~100 km long, and about 70 km

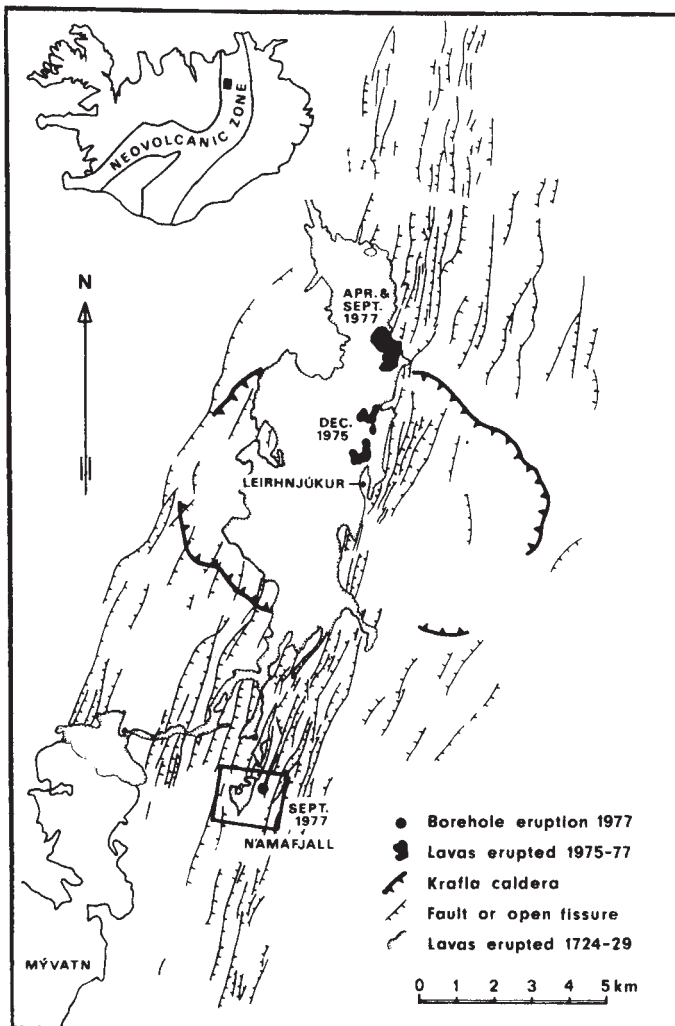


Fig. 1 The main geological features of the Krafla area and location of the eruptions 1975-77. The Námafjall area is shown in greater detail in Fig. 2. Adapted from a map by Kristján Saemundsson¹.

have been activated with horizontal widening of 2-3 m in places. Magma is being continuously fed (about $5 \text{ m}^3 \text{ s}^{-1}$) into magma reservoirs below the Krafla caldera (Fig. 1) at a depth of about 3 km, as indicated by seismic and ground deformation evidence¹.

The rifting activity takes place in short events where 5-15 km long segments of the fault swarm are activated with movements on faults, earthquakes and the formation of new steam fields. This is accompanied by subsidence of a large area with a centre within the Krafla caldera caused by magma movement into the fault swarm.

Three small lava eruptions have accompanied the eight rifting events that have taken place, but all three eruptions were in the vicinity of the magma reservoirs and so far only the eruption through the borehole has provided samples of the magma actually moved into the fault swarm.

The total volume of magma moved into the fault swarm is about $3.9 \times 10^8 \text{ m}^3$, while the volume of the lavas is about $2.4 \times 10^6 \text{ m}^3$ or 0.6%.

The first eruption, on 20 December 1975, took place near the centre of the caldera (Fig. 1) although the main rifting occurred 45 km to the north. The second eruption, on 27 April 1977, took place near the northern rim of the caldera (Fig. 1), while the main rifting occurred about 10 km to the south of the caldera centre.

In the third eruption, on 8 September 1977, the main outflow of lava was again near the northern rim of the caldera, while the

main rifting took place south of the caldera, just north of the Námafjall geothermal field. We give here a short account of this event and the borehole eruption.

8 September deflation/rifting event

The deflation and rifting of 8 September 1977 started with a volcanic tremor recorded on seismographs at 15.47 h and about the same time the centre of the caldera started deflating. Just before 18.00 h a lava eruption started near the northern rim of the Krafla caldera (Fig. 1). According to the pilots of an overflying aeroplane, its first sign was a white column of steam darkening at the base after a few minutes. Shortly afterwards lava spattering started from a short segment of the fissure, which rapidly extended to a total length of 800 m. The lava output increased quickly, reaching maximum in less than about 30 min, and by 19.30 h most of the lava was already erupted. By 22.30 h the activity had died out. Assuming that the magma started to ascend when volcanic tremor appeared on the seismometers and deflation on the tiltmeter, the rate of ascent is about 0.5 m s^{-1} assuming a depth of 3 km for the magma reservoirs.

The deflation rate soon decreased and stopped temporarily at about 17.20 h. Deflation started again at about 18.20 h. This was the main deflation and most likely related to the magma movement to the south. The centre of the rifting segment in this event was just north of the Námafjall geothermal field (Fig. 1). Some overlap exists between this rifting segment and that rifted in the previous event on 27 April 1977, as reference lines across the rift zone that already had increased in length by 2 m extended a further 1 m on 8 September⁴.

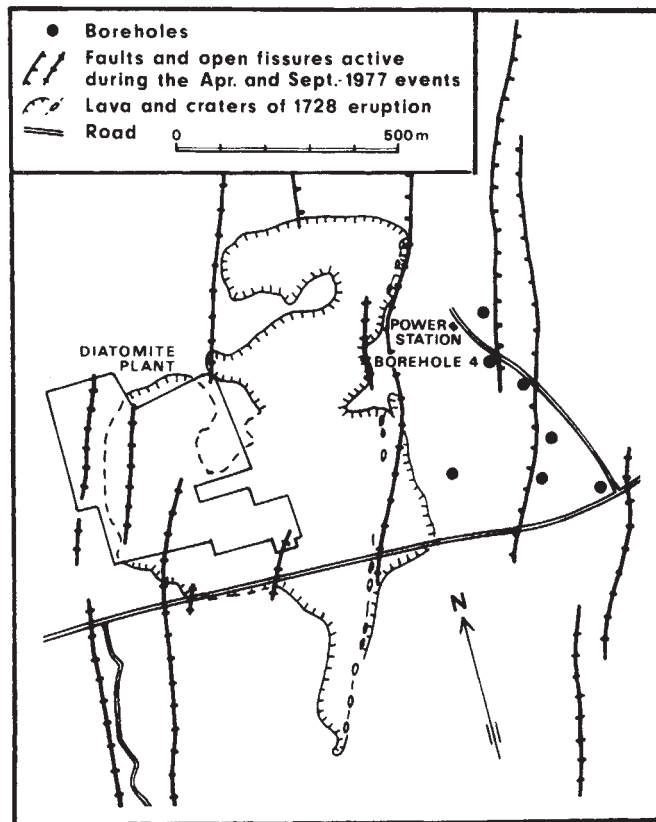


Fig. 2 Sketch map of the Námafjall area from an aerial photograph of 9 September 1977. The location of boreholes is shown by dots. The faults shown on the map have all been active in the recent events. For location see Fig. 1.

At Námafjall the first observed sign of the rifting event was movement of faults crossing a road (Fig. 2) at about 22.40 h. Assuming that the main magma movement to the south started at 18.20 h and with the distance of 9 km from Leirhnjúkur at the centre of the caldera, the rate of horizontal movement is about 0.6 m s^{-1} . A similar velocity was derived for magma movement in the April 1977 deflation/rifting event³. The figures for vertical and horizontal movement of the magma are strikingly similar to the figures (0.6 m s^{-1}) arrived at for the maximum rate of magma ascent in the Askja eruption 1961 and the Lakagígar eruption of 1783⁵, and there are indications that the magma ascended with similar velocity during the Eldfell eruption 1973 (ref. 6, p 30).

The eruption through the borehole began about one hour later, at 23.45 h. The rate of ground deflation decreased rapidly, and at about 05.00 h on 9 September deflation had stopped and the centre of the caldera was inflating again.

The borehole eruption

The Námafjall geothermal field lies on the Krafla fault swarm 9 km south of the centre of the Krafla caldera. The five boreholes in use for steam extraction are spaced with the distance of 80–200 m (Fig. 2) and extend down to 650–1,800 m with casing extending down to 500–600 m. The deepest hole has an additional slotted liner down to the bottom at 1,800 m. The boreholes are situated in a highly faulted area and deliberately placed to intersect faults at favourable depths.

The eruption took place through borehole number 4, drilled in 1968. It is 1,138 m deep, has 7" casing down to 380 m and 5" casing down to 625 m. The diameter from 625 to the bottom is 6.25" and this part has no casing or liner. The main aquifers are reported at 638 and 1,038 m (ref. 8). The average temperature of the inflowing water is estimated at 251–256 °C (ref. 7). The total discharge of the borehole at the time of eruption is not known accurately, but from measurements in 1971⁸ and the estimated inflow temperature, the total discharge of water–steam can be estimated at 30 kg s^{-1} at about 7 bar absolute well head pressure. This assumes that the inflow is water only and

that steam is generated in the borehole during its ascent. (If the inflow is a steam–water mixture a lower value results.) The superstructure of the borehole suffered minor damage due to the eruption and the borehole continued to produce steam at a similar rate as before. Following the eruption there was a marked increase in fumarolic activity in the area around the boreholes, which later decreased markedly.

Movements on faults in the Námafjall area were first noted at about 22.40 h, when the main road through the area was cut through and became impassable. By that time the eruption that had taken place 12 km to the north was finished and further activity to the south was anticipated. It was already dark, and with the steam from the boreholes drastically affecting visibility, conditions at Námafjall were confusing.

An examination of the earthquake activity shows a southward migration from the caldera along the fault swarm. The earthquake activity reached the Námafjall area shortly before 22.00 h (ref. 9).

The description below is compiled from accounts of 10 people, each of whom saw only a part of the event.

The whole event lasted between 15–25 min. It can be divided into three stages. The first phase was best observed from the main road about 400 m south of borehole 4. At approximately 23.45 h an explosion in the borehole field was heard and a thin incandescent column, about 15–25 m in height, was seen. The column widened slightly upwards and sparks and cinders were continuously shot from it. This phase of the eruption, accompanied by a continuous roar, lasted no longer than 1 min.

During the second phase, lasting the next 10–20 min, there was little or no activity at the eruption site. Occasional red flashes may have occurred during the latter part of this phase, according to some of the observers, but could also belong to the final phase.

The final phase consisted of a series of very rapid explosions or shots of glowing scoria. A few groups of explosions were observed each consisting of several individual shots (Fig. 3a). The total length of the final phase is estimated at about 1 min. During this phase the exact location of the eruption was established, when it was discovered that the pipe directly above the hole conducting the steam–water mixture had been ruptured by the eruption (Fig. 3b). It is not known whether the steam–water

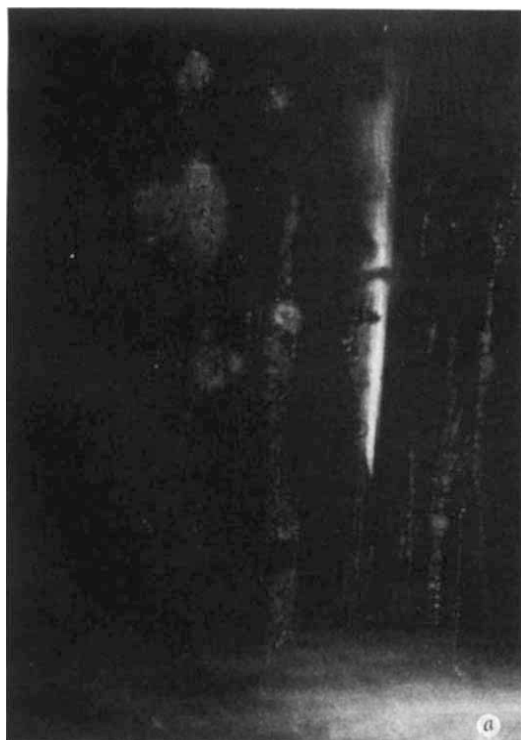


Fig. 3 *a*, The eruption through borehole 4 at Námafjall on 8 September 1977. The picture was taken just about midnight at the distance of 50–70 m. The explosion lasted about 1 s. By comparison with the tool shed on the left the height of the eruptive column is estimated at 13–15 m. Photo Hördur Vilhjálms-son. *b*, Borehole 4 at Námafjall, on the morning of 9 September 1977. The steam jet is emitted through the rupture in the pipe created by the volcanic eruption. The steam–water separators are housed in the shed to the left. Practically the same scale as in Fig. 3a. Photo Sigurdur Thorarinnsson.

output was cut off at any time during the eruption, but during the second phase red flashes were seen in the steam-water mixture emitted through the ruptured knee on the pipe.

The magma was apparently injected into the hole through a steeply dipping fault intersecting the borehole above the aquifer at 1,038 m and most probably below the casing at 625 m as steam production continued after repairs of the superstructure. At the surface substantial movements on faults near the borehole were observed.

Products of the eruption

The eruption produced a tiny sheet of tephra (scoria and cinders). An area about 50 m long and of 25 m maximal width was covered by continuous layer, but single grains could be traced to at least 150 m north of the borehole. The tephra was very loosely packed and unevenly distributed and thickness estimates are uncertain, especially away from the borehole. Maximum thickness was 8–10 cm at a distance of 15–20 m.

The volume of the total output is estimated at 26 m³. The density of the deposit was roughly calculated at 0.12 g m⁻³ and the total weight of the deposit at 3,100 kg. The volume of the magma erupted is therefore 1.2 m³ using 2.7 g m⁻³ as the density of the magma.



Fig. 4 The borehole scoria. From the right: a large scoria fragment (type 1) showing a chilled, crusted surface. The edges curled up when the original piece broke and show frothy glass formed from the molten interior. Fragments (type 2) formed from the interior of larger pieces, deformed to various degrees. Some show relatively little deformation while others form spindles and small spheres. Two scoria pieces with a protrusion (type 3). The bread crust part is formed by the initial chilling and the spherical protrusion later from the still molten interior.

The tephra is greyish-black in colour and coarse grained. Median (ϕ 50) grain size in a sample collected 20 m from the 'vent' is -4.2ϕ (18.4 mm). As the largest clasts break very easily, this is likely to be an underestimate. Grains smaller than 1 mm are scarce.

The clasts (Fig. 4) can be divided into three types: (1) clasts with 2–4 mm thick, cracked, black, glassy crust ('bread crust') on one side and glass froth on the other. (2) Grains made entirely of torn glass froth of various shapes and sizes. (3) Crusted clasts of various sizes and shapes, each with a neat frothy sphere protruding from one end.

There are gradations between the different types of clasts making it possible to establish how they were formed. On injection into the borehole, the magma seems to have formed

Table 1 Microprobe analysis of the products from the eruption of borehole 4 at Námafjall, 8 September 1977

Composition of the glass									
SiO ₂	TiO ₂	Al ₂ O ₃	FeO ^t	MnO	MgO	CaO	Na ₂ O	K ₂ O	P ₂ O ₅
50.0	2.24	12.7	14.9	0.24	5.16	10.3	2.34	0.37	0.23
Plagioclase									
SiO ₂	Al ₂ O ₃	FeO ^t	CaO	Na ₂ O	K ₂ O	Total	An		
52.9	29.0	1.20	13.2	4.03	0.09	100.4	75.9		
Olivine									
SiO ₂	FeO	MnO	MgO	CaO	NiO	Total	Fo		
37.7	25.7	0.35	35.7	0.29	0.13	99.9	71.2		
Pyroxene									
SiO ₂	TiO ₂	Al ₂ O ₃	FeO	MnO	MgO	CaO	Na ₂ O	Cr ₂ O ₃	Total
49.8	1.09	3.76	11.5	0.34	16.1	16.2	0.22	0.28	99.3

lumps of various shapes and sizes. Some of the smaller lumps survived all the way to the surface where they ripped open, and small, rounded protrusions formed from the molten interior. The larger lumps seem to have broken at various depths. The incandescence of the column indicates that most of them disintegrated within the upper levels of the borehole. Clasts with glassy crust on one side were formed from the cooled exterior of the lumps, while the molten interior disintegrated into fragments of twisted glass froth.

Assuming that the bulk of the magma was injected into the hole during the two 1-min periods, the intrusion rate is about 25 kg s⁻¹, which is of the same order as the amount of steam-water production of the borehole. Using the heights between 20 and 40 m velocities between 20 and 30 m s⁻¹ are obtained. This means that if the magma was injected at 1,000 m depth it took 0.5–1 min for it to reach the surface.

Chemistry and petrology of the magma

The scoria produced in the borehole eruption is extremely vesicular and composed almost entirely of glass. There are very occasional microphenocrysts of plagioclase, olivine and augite, always less than 0.2 mm in length. Average chemical analysis of the glass and the mineral phases are given in Table 1. The minerals seem to be in equilibrium with the liquid at the time of cooling¹⁰.

Temperature estimates at the time of chilling give 1,153 °C from the olivine-glass composition¹¹ and, 1,158 °C for the plagioclase-glass composition¹².

The chemical composition of the borehole products differs significantly from that erupted a few hours earlier 12 km to the north, but has similar composition as the lavas erupted at the beginning of the rifting on 20 December 1975¹⁰.

Observations made by the following were used in compiling this report: Ágúst Hilmarsson, Árni Ingólfsson, Baldur Thorsteinsson, Benedikt Sveinbjörnsson, Fridrik Steingrímsson, Gestur Gíslason, Hjörtur Tryggvason, Hrefna Kristmannsdóttir, Ómar Sigurdsson, Thorfinnur Finnlaugsson.

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Thrombin-stimulated cell division involves proteolysis of its cell surface receptor

Kevin C. Glenn & Dennis D. Cunningham

Department of Microbiology, College of Medicine, University of California, Irvine, California 92717

A cell-surface component of molecular weight 43,000 is cleaved by thrombin on cells that divide after thrombin treatment, but is not cleaved on cells that are unresponsive to its mitogenic action. Studies with a photoreactive derivative of thrombin showed that its cell surface receptor has a molecular weight of 43,000. This indicates that thrombin must cleave its receptor to stimulate cell division.

STUDIES on the mechanism of the mitogenic action of thrombin have been facilitated by its ability to bring about cell division in serum-free cultures of non-dividing chick embryo (CE), mouse embryo (ME) or human foreskin (HF) cells¹⁻³. This allows experiments to be conducted in chemically defined culture conditions. Also, thrombin possesses a well characterised enzymatic activity which is necessary for stimulation of cell division^{2,4}. This makes it feasible to look for specific biochemical events that it must produce so as to bring about cell proliferation.

The first step was to establish the cellular site of thrombin action. Although thrombin is internalised by CE cells in mitogenic conditions^{5,6}, we recently demonstrated that internalisation is not necessary and that its action at the cell surface is sufficient to cause CE cells to divide⁷. This led us to examine the cell surface for events that are involved in thrombin-stimulated cell division. One such event is the binding of ¹²⁵I-thrombin to a specific cell surface receptor⁸. Scatchard analysis of the binding data to ME cells indicated a single class of high affinity receptors. It seems that thrombin must bind to its receptor to cause cell division, as small amounts of serum inhibited both the binding of thrombin to its receptor and its ability to stimulate cell division without reducing its proteolytic activity or its nonspecific association with the cells⁸.

In the present study, we radiolabelled the thrombin receptor and obtained evidence that thrombin must cleave it to stimulate cell division. The receptor was labelled using a photoreactive cross-linking derivative of ¹²⁵I-thrombin. The amount of cross-linked complex formed was proportional to the amount of specific binding, indicating that the labelled component was the cell surface receptor for thrombin. The molecular weight of the receptor was 43,000, equal to that of a cell surface component which other experiments indicated thrombin must cleave to stimulate cell division. In these experiments, we labelled cell surface proteins with lactoperoxidase and ¹²⁵I⁻ and found that a 43,000-dalton cell surface component (43 K) was present on CE cells that were responsive to the mitogenic action of thrombin and also on four separately isolated populations of CE cells that did not divide after thrombin treatment. However, 43 K was cleaved by thrombin only on the responsive cells; it was thrombin resistant on the four unresponsive populations. Thus, cleavage of 43 K by thrombin seems to be necessary for thrombin-stimulated cell division. These separate approaches suggest that a 43,000-dalton cell surface protein initiates a mitogenic signal by binding thrombin and undergoing thrombin-mediated proteolysis.

CE cells that are unresponsive to the mitogenic action of thrombin

To determine the events which cause thrombin-stimulated cell division, it was important to compare the effects of thrombin on both cells that divide and those that do not divide after thrombin treatment. An event which occurs in the responsive but not the unresponsive cells can be further studied as a possible necessary step in thrombin mitogenesis. The procedure for obtaining unresponsive cells was based on our finding that during serial subculture of CE cells, they lose virtually all of their response to the mitogenic action of thrombin or trypsin, but retain responsiveness to serum³. By the 25th population doubling, we found in four separate isolates a loss of about 80% or 90% of the mitogenic response to thrombin or trypsin, respectively (Fig. 1). This loss was not dependent on the method used to subculture the cells during the 25 population doublings, as unresponsive population I (Fig. 1b) was subcultured using 0.01% chymotrypsin whereas unresponsive population II (Fig. 1c) was sub-

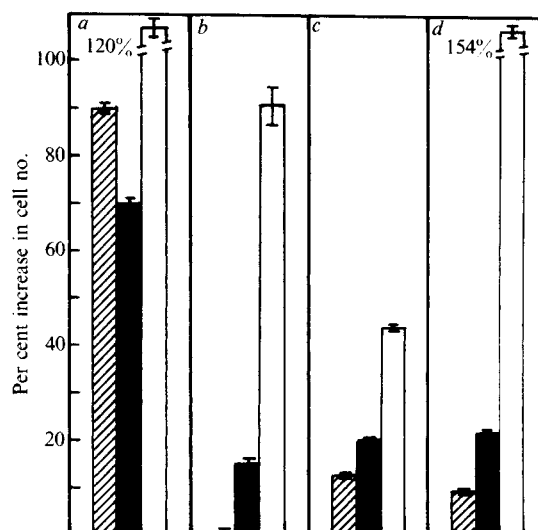


Fig. 1 Comparison of cell number increases of responsive cells with two different unresponsive cell isolates. Cultures of nondividing CE cells in serum-free medium were set up as previously described³. The indicated mitogen was added and cell number was measured 24 h (a-c) or 48 h (d) later. The data shown are means of duplicate determinations obtained with a Coulter electronic particle counter. Error bars show one standard deviation from the mean. Hatched bars, trypsin ($3 \times$ recrystallised, 247 units mg^{-1} (Worthington)) was added to $0.2 \mu\text{g ml}^{-1}$. Solid bars, highly purified human thrombin (about 3,000 NIH units mg^{-1})¹⁷ was added to $3.0 \mu\text{g ml}^{-1}$. Open bars, chicken serum (Irvine) was added to 5.0%. a, secondary CE cells; b, CE cells at population doubling 26 (passage 13) which had been subcultured using chymotrypsin (0.01%) in phosphate-buffered saline (PBS) (unresponsive population I); c and d, CE cells at population doubling 28 (passage 14) which had been subcultured using trypsin (0.05%) and EDTA (0.02%) in PBS (unresponsive population II).

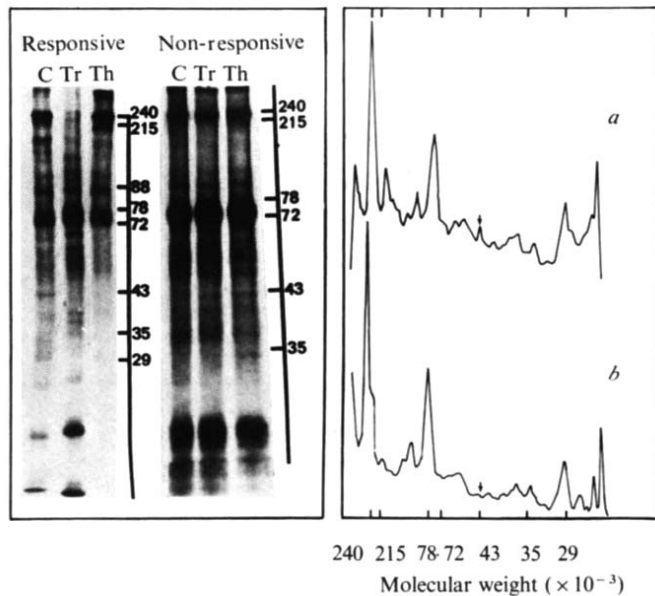


Fig. 2 Analysis of cell surface of responsive cells with or without exposure to thrombin or trypsin. Cell surface proteins were labelled by lactoperoxidase-catalysed iodination with $^{125}\text{I}^-$ (ref. 9). Cell monolayers were rinsed five times with Dulbecco's PBS and incubated for 5 min at 22°C with 6 IU ml^{-1} lactoperoxidase (Calbiochem), 6 U ml^{-1} glucose oxidase (Calbiochem), 0.5 mCi ml^{-1} carrier free $^{125}\text{I}^-$ and 10 mM glucose in Dulbecco's PBS. The cells were then rinsed five times with ice cold calcium and magnesium-free PBS and solubilised and boiled for 3 min in 0.1 M Tris-HCl ($\text{pH } 6.8$) containing 1.0% SDS, 1.0% 2-mercaptoethanol, 5.0% glycerol and bromophenol blue. The samples were electrophoresed using $7.5\text{--}15\%$ linear gradient SDS-polyacrylamide slab gels¹⁰. Molecular weights were determined by electrophoresing human red blood cell membrane samples²² in slab gel lanes adjacent to the ^{125}I -labelled samples. Autoradiography was performed by exposing Kodak XR-5 X-ray film to dried Coomassie blue-stained gels. Left, autoradiograms of cell surface proteins from responsive and unresponsive (population II of Fig. 1) cells that were untreated (lanes C), treated for 24 h with $3.0 \mu\text{g ml}^{-1}$ thrombin (lanes Th) or treated for 24 h with $0.2 \mu\text{g ml}^{-1}$ trypsin (lanes Tr) before iodination of cell surface proteins. Right, densitometric scans of autoradiograms from responsive untreated cells (a) and from responsive thrombin-treated cells (b). The arrows indicate the position of the $43,000 \text{ MW}$ marker.

cultured with 0.05% trypsin in 0.02% EDTA. The loss of responsiveness did not result simply from a slower response to protease stimulation, as doubling the length of exposure to thrombin or trypsin from 24 h to 48 h did not increase the amount of cell division (Fig. 1c, d). Also, the loss of responsiveness was not due to a shift in the effective mitogenic dosage of thrombin on the CE cells, as they were serially subcultured. Figure 3 shows that the cells at population doubling 25 remained unresponsive even after exposures to high thrombin concentrations.

In contrast, CE cells at population doubling 25 remained responsive to the mitogenic action of serum. Although the response was reduced if cell number was measured 24 h after serum addition, there was more than a cell doubling by 48 h (Fig. 1d). ^3H -thymidine autoradiography showed that by 48 h all of the cells had synthesised DNA, demonstrating that the cell number increase did not represent multiple divisions of only a small subpopulation of cells (unpublished results). Together, these results show that by population doubling 25, CE cells lost most of their mitogenic response to thrombin or trypsin. However, they retained a full but delayed response to the mitogenic action of serum.

Cleavage by thrombin of a $43,000\text{-dalton}$ cell surface component from responsive but not unresponsive CE cells

These results made it possible to look for cell surface components that were cleaved by thrombin on responsive CE cells but which were thrombin resistant or absent on the unresponsive cells. Cell surface proteins were examined on thrombin-treated and untreated cells by lactoperoxidase-catalysed iodination with $^{125}\text{I}^-$ (ref. 9) followed by SDS-polyacrylamide gel electrophoresis¹⁰ and autoradiography. We also examined trypsin-treated and untreated cells, as trypsin is a potent mitogen for CE cells^{3,11-14} and can produce cell division as a result of action at the cell surface¹⁵. Figure 2 shows that 43 K was present on responsive secondary CE cells and also on CE cells at population doubling 25 that were unresponsive to the mitogenic action of thrombin or trypsin. As shown, 43 K was removed from the responsive cells by mitogenic treatments with either thrombin or trypsin. However, in four separately isolated populations of unresponsive CE cells, 43 K was not removed by these thrombin or trypsin treatments. Figure 2 shows that this could be determined by either visual examination of autoradiograms of the gels or densitometric scans of the autoradiograms. Stimulation of division of non-dividing secondary CE cells by insulin or serum did not remove 43 K from the cell surface (unpublished results). Thus, its removal was not simply a consequence of stimulating cell proliferation. DFP (di-isopropylfluorophosphate)-inactivated thrombin is non-mitogenic⁴ and does not remove 43 K from responsive cells (unpublished results). Together, the above results indicate that cleavage of 43 K is necessary for thrombin-stimulated cell division and that its cleavage is due to thrombin rather than a cellular protease.

It was important to ensure that 43 K was not a serum protein or an intracellular component. It is unlikely to be a serum protein as the cells were extensively rinsed free of serum and placed in serum-free medium for 48 h before labelling with $^{125}\text{I}^-$.

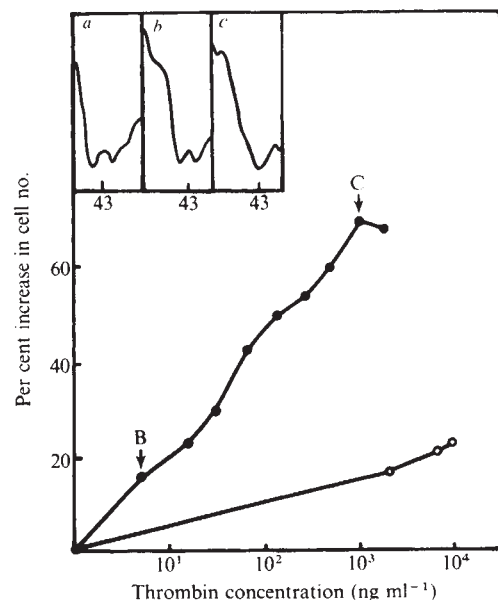


Fig. 3 Effect of thrombin concentration on cleavage of 43 K and initiation of cell division. The main figure shows the per cent increase in cell number for responsive secondary CE cells (●) and unresponsive cell population II (○) following a 24-h exposure to the indicated concentrations of thrombin. The insets show densitometric scans of autoradiograms of ^{125}I -labelled cell surface proteins of responsive cells electrophoresed as in Fig. 2. The $30,000\text{--}60,000$ molecular weight regions of the scans are shown with the position of the $43,000$ molecular weight marker. Responsive CE cells were either untreated (inset a), or treated with 5.0 ng ml^{-1} thrombin (inset b) or $1.0 \mu\text{g ml}^{-1}$ thrombin (inset c) for 24 h before labelling cell surface proteins as in Fig. 2.

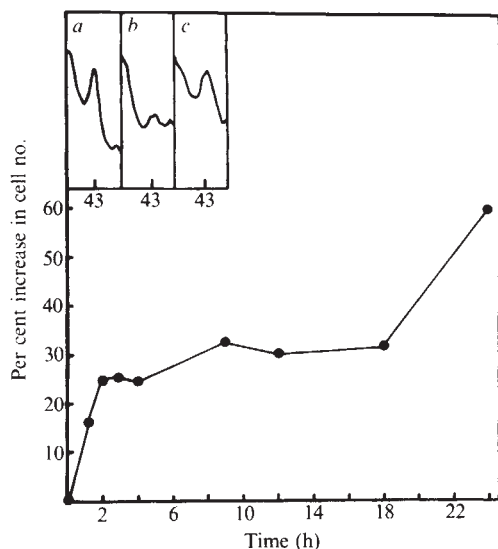


Fig. 4 Effect of length of thrombin treatment on stimulation of cell division and cleavage of 43 K in responsive CE cells. The main figure shows the cell number increases after treating non-dividing cultures with $3.0 \mu\text{g ml}^{-1}$ thrombin for the indicated times, rinsing the cultures and continuing incubation in thrombin-free medium from parallel cultures. Cell number was measured 24 h after the initial exposure to thrombin. Measurements at 72 h showed that the observed low responses after short thrombin treatments were not a result of delayed increases in cell number (unpublished results). The insets show densitometric scans of 43 K as in Fig. 3. Inset *a*, control cells not treated with thrombin; inset *b*, cells were labelled after a 7-h treatment with $3.0 \mu\text{g ml}^{-1}$ thrombin; inset *c*, like inset *b*, except the cells were incubated for 3 h in thrombin-free medium following the 7-h thrombin treatment but before surface labelling.

and lactoperoxidase. More important, if it were a serum protein, it would have to be one that is sensitive to thrombin and trypsin after binding to responsive cells, but resistant to cleavage by these proteases after binding to the unresponsive cells. Also, 43 K does not seem to be an intracellular protein. It was not labelled by ^{125}I in the absence of lactoperoxidase, and it was removed by thrombin treatments as short as 1 h. Although some thrombin would be internalised by that time, it would probably be in endocytic vesicles and would not have access to cytoplasmic proteins.

Removal of 43 K from responsive cells by mitogenic but not non-mitogenic thrombin treatments

To further test the relationship between cleavage of 43 K and the stimulation of cell division by thrombin, we attempted to dissociate the two events by varying the concentration of thrombin. The condition most likely to dissociate cell division from removal of 43 K by thrombin is to expose cells to the highest concentration of thrombin which is not mitogenic. Figure 3 shows that the highest concentration of thrombin that did not produce significant cell division was 5 ng ml^{-1} . As shown in Fig. 3, inset *b*, this concentration did not bring about a detectable change in 43 K. However, inset *c* shows that a maximally mitogenic concentration of thrombin removed 43 K. Intermediate concentrations gave incomplete removal of 43 K.

Replacements of 43 K after thrombin treatment seems to prevent cell division

Figure 4 shows that maximal stimulation of CE cell division by thrombin required continued exposure during the 24-h period; shorter exposures resulted in smaller increases in cell number measured either at 24 h or 72 h. An apparent dissociation between removal of 43 K and stimulation of cell division by

thrombin is shown in Fig. 4 where a 7-h treatment with $3 \mu\text{g ml}^{-1}$ thrombin removed 43 K (inset *b*) but produced only a $\sim 30\%$ increase in cell number by 24 h. This suggested that cleavage of 43 K by thrombin was not sufficient to achieve maximal thrombin-stimulated cell division. However, inset *c* shows that 43 K was replaced in the cell membrane within 3 h if thrombin was removed after the 7-h treatment. This suggests that replacement of 43 K stops the events leading to cell division and that maximal stimulation of cell division requires continuous removal of 43 K. An alternative possibility is that thrombin releases a specific fragment of 43 K that is a positive effector, the continuous production of which is required to produce maximal cell division. By studying the effects of non-mitogenic proteases on 43 K, it might be possible to determine whether 43 K is a positive or a negative effector molecule.

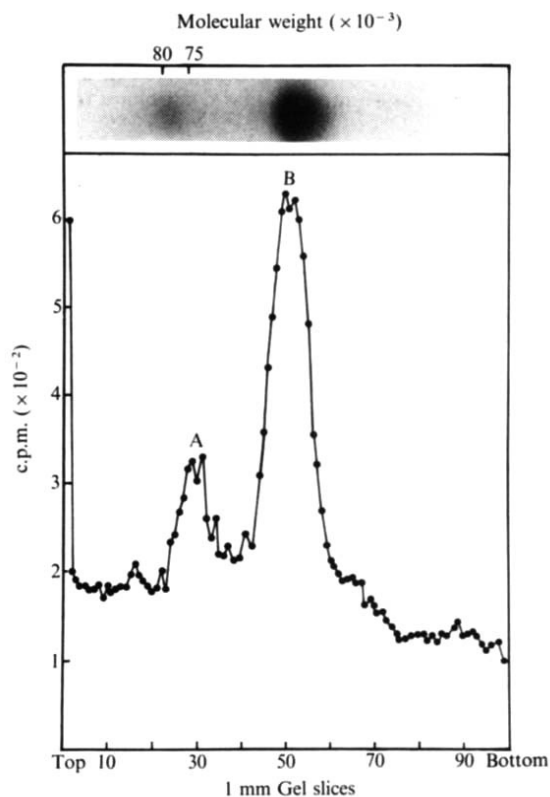


Fig. 5 Labelling of the thrombin receptor with a photoreactive derivative of ^{125}I -thrombin. Details of the preparation of NAPEDE- ^{125}I -thrombin and the methods to photoaffinity label the thrombin receptor will be described elsewhere¹⁶. The general protocol for this experiment is described in the text and was based on previous studies with the epidermal growth factor receptor²³. After cross-linking the ^{125}I -thrombin to its receptor, the cells were solubilised in 1.0% SDS and 1.0% 2-mercaptoethanol at 60°C for 30 min and cellular proteins were electrophoresed in 7.5% polyacrylamide tube gels containing 0.1% SDS. The line drawing shows the radioactivity in 1.0-mm slices of the gel. The inset autoradiogram shows the radioactivity in a 7.5–15% linear gradient slab gel following electrophoresis of a similarly labelled sample. The position of 80,000 and 75,000 molecular weight marker proteins are shown for this autoradiogram.

Evidence that 43 K is the thrombin receptor

As stimulation of cell division by thrombin seems to require both binding to its receptor⁸ and cleavage of 43 K, it was important to determine the relationship, if any, between the thrombin receptor and 43 K. Indeed, a relationship was suggested by the following experiments which showed that the thrombin receptor has the same molecular weight as 43 K.

As described elsewhere¹⁶, a photoactivable cross-linking derivative of ^{125}I -thrombin was prepared by covalently linking it

to *N*-(4-azido-2-nitrophenyl)ethylenediamine (NAPDE). The NAPDE-¹²⁵I-thrombin bound to cells like ¹²⁵I-thrombin¹⁶, with 60% of the total binding to specific receptors at a ligand concentration of 50 ng ml⁻¹. We then incubated CE cells with 50 ng ml⁻¹ NAPDE-¹²⁵I-thrombin for 2 h at 22 °C, rinsed away unbound reagent, treated the cells for 5 min with UV light and solubilised and electrophoresed the cellular proteins in SDS-polyacrylamide gels. Figure 5 shows the radioactivity in the gel slices from such an experiment. Peak B co-migrated with NAPDE-¹²⁵I-thrombin that had not been reacted with the cells. Peak A represents a high molecular weight cross-linked complex. Two lines of evidence showed that this complex was formed between NAPDE-¹²⁵I-thrombin and the cell surface receptor for thrombin. First, the complex was not formed in the absence of cells; thus, it was not simply intermolecular complexes of NAPDE-¹²⁵I-thrombin. Second, addition of unlabelled thrombin caused parallel declines in the amount of specific binding and the amount of cross-linked complex formed, indicating a direct relationship between the thrombin receptor and the cross-linked cellular component (unpublished results).

We estimated that the molecular weight of the cross-linked complex was 79,000 (Fig. 5). The NAPDE-¹²⁵I-thrombin had an apparent molecular weight of 36,000. Subtracting this from the molecular weight of the complex leaves a cellular receptor of 43,000 daltons. Thus, on the basis of their apparent molecular weights, the cell surface receptor for thrombin seems to be identical to 43 K described above that was identified by labelling cell surface proteins with ¹²⁵I⁻ and lactoperoxidase.

Other cell surface events involving thrombin

We recently found that a significant fraction of ¹²⁵I-thrombin that is specifically bound to the surface of HF cells becomes linked to the thrombin receptor by a linkage that is apparently covalent¹⁸. This occurs in the absence of a cross-linking reagent. More linkage occurs with NAPDE-¹²⁵I-thrombin, although this increment depends on the cell type (unpublished results). By studying the occurrence of the direct linkage of thrombin to its receptor in responsive and unresponsive cells, it should be possible to evaluate its role in thrombin-stimulated cell division.

The treatment of mouse splenocytes with thrombin removes a cell surface component of 45,000 daltons that was suggested to be the histocompatibility antigen¹⁹. Although its role in the stimulation of splenocytes by thrombin was not examined, it might correspond to 43 K examined here. Another cell surface component that is sensitive to thrombin is one with a molecular

weight of 205,000 (205 K) on CE cells²⁰. This component was removed by both mitogenic and non-mitogenic proteases²¹. Thus, it is not simply a negative effector molecule whose removal from the cell surface is sufficient to stimulate cell division. On the other hand, the above results are consistent with the possibility that proteolysis of 205 K by thrombin produces a specific peptide that is a positive signal in or on the cell. In our experiments, 205 K was not labelled or resolved clearly enough to allow a meaningful examination of it. In future studies, it will be important to use other techniques to label cell surface proteins and to separate them on two-dimensional gels. This should allow us to study the possible involvement of 205 K in thrombin-mediated cell division and to determine if it or other cell surface components are thrombin sensitive in responsive cells but either absent or thrombin resistant in cells that do not divide after thrombin treatment. Such an attempt seems worthwhile as the requirement for at least several hours' exposure to thrombin to produce a detectable increase in cell number might reflect the need for several perhaps interdependent cell surface interactions with thrombin to produce cell division.

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Distribution of polymorphic forms of troponin components and tropomyosin in skeletal muscle

G. K. Dhoot & S. V. Perry

Departments of Immunology and Biochemistry, University of Birmingham, PO Box 363, Birmingham, UK

Specific antibodies have been used to show that in adult skeletal muscle the slow and fast forms of the components of the troponin complex are located in type I and type II fibres respectively. α -Tropomyosin is restricted to type II cells. During development, as a result of changes in innervation and in certain diseased stages, both the slow and fast polymorphic forms of the troponin components are present in the same cell.

MYOFIBRILLAR proteins are known to exist in several different forms, and the complement of these proteins present in striated muscle depends on the activity pattern of the tissue. For example, it has long been appreciated that myosins of differing ATPase activities and light chain composition are associated with fast skeletal, slow skeletal and cardiac muscles. The differential staining for myosin ATPase at different pH values implies that different types of myosin are located in each of the main fibre types of which skeletal muscle is composed¹. Electrophoretic studies of the myosin light chain components in

samples obtained from single fibres² and investigations with fluorescent antibodies^{3,4} have now confirmed that in adult skeletal muscle the fast and slow forms of myosin exist in different cells. The situation with myosin is, however, complicated, as study of its light chain composition suggests that the fast and slow isoenzymic forms of this protein may each also exist in at least two forms. For example, the alkali light chains A1 and A2 of fast skeletal muscle myosin are both present in type II fibres²⁻⁶. Therefore, if the myosin exists as homodimers (that is, each head is identical) there will be two isoenzymic forms in each cell type and three if the heterodimer possessing different alkali light chains in each head is present in addition to the homodimers. Further, there is evidence to suggest that these forms may also possess different actin-activated ATPase activities^{7,8}.

Although there is a good correlation between the type of myosin present and the speed of contraction of skeletal muscle⁹, the characteristics of the overall response to stimulation must also depend on several other factors. One of these is the nature of the regulatory proteins of the myofibril—troponin C, troponin I, troponin T and tropomyosin. The function of these proteins is to determine the way in which the myofibrillar ATPase responds to the rise in intracellular Ca^{2+} concentration that occurs during stimulation. As judged by criteria such as amino acid composition, electrophoretic mobility, complex formation and sequence studies, troponin I^{10,11}, troponin T¹²⁻¹⁴, troponin C¹⁷⁻¹⁹ and tropomyosin^{21,22} exist in striated muscles in polymorphic forms with different properties and structure. Different forms of troponin I are present in fast skeletal, slow skeletal and cardiac muscles. Although it has not been as intensively studied as troponin I the evidence available suggests that troponin T probably also exists in different forms in each type of striated muscle. Two types of troponin C have been isolated from human skeletal muscle²³ and cardiac troponin C has been reported to differ from the form present in fast skeletal muscle¹⁹. Most adult skeletal muscles are of mixed type and contain the two forms of each of the troponin components that are characteristic for the two types of skeletal muscle. Likewise the proportions of α and β tropomyosin in skeletal muscle vary according to the speed of the muscle²². The proportions of the two forms of each protein of the regulatory system present in the whole muscle are, in general, roughly that which would be expected from the ratio of the numbers of type I and type II fibres present, but not always so²⁴.

Thus the presumptive skeletal muscle cell has the capacity to synthesise several different forms of each of the myofibrillar proteins. From the information currently available about the polypeptide compositions of actin, myosin, tropomyosin and the troponin complex of rabbit skeletal muscle, about 22 structural genes are involved in the synthesis of these proteins. At any one time, in a given cell type, only 8 genes from this pool need to be expressed to produce a single form of each of these myofibrillar proteins (see ref. 25).

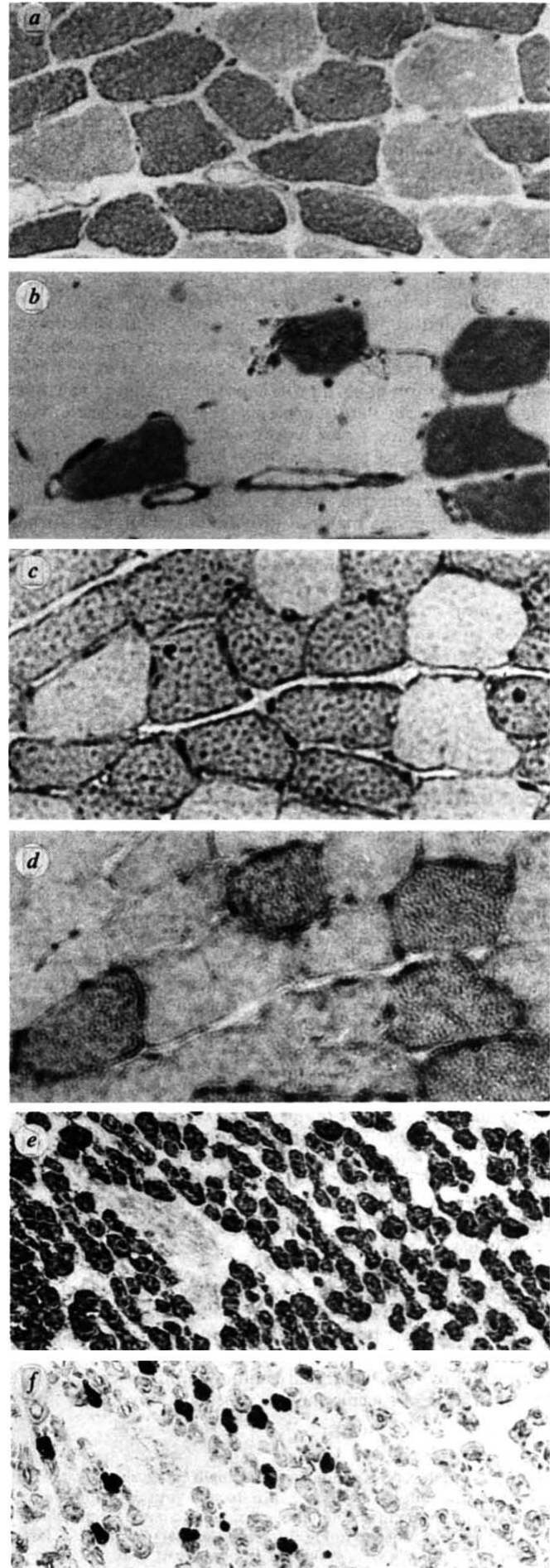


Fig. 1 Distribution of fast and slow skeletal forms of troponin I in sections of adult and 2-day-old mouse muscle. Unfixed tissue sections (6 μm thick) were stained with $\frac{1}{20}$ dilution of the antiserum and the antibody localised with sheep anti guinea pig IgG labelled with type VI horseradish peroxidase^{32,37,38}. Stained for ATPase according to the method of Padykula and Herman¹ as described by Dubowitz and Brooke³⁹. The granular appearance and distribution of the stain (also see Figs 2 and 3) is a consequence of the conditions selected to obtain optimal staining for study by optical microscopy. The distribution of granules therefore does not accurately indicate the location of the myofibrils to which the antibodies are attached. *a* To *d* are serial sections of adult and *e* and *f* serial sections of 2-day-old mouse gastrocnemius muscles. *a*, ATPase at pH 9.4; *b*, ATPase at pH 4.2; *c*, immunoperoxidase with anti-fast skeletal troponin I; *d*, immunoperoxidase with anti-slow skeletal troponin I; *e*, immunoperoxidase with anti-fast skeletal troponin I (2-day-old); *f*, immunoperoxidase with anti-slow skeletal troponin I (2-day-old); $\times 200$.

As a first approach to understanding the mechanisms that regulate the complex gene pool responsible for myofibrillar protein synthesis in skeletal muscle, we have attempted to answer the following questions: (1) Are each of the two polymorphic forms of the components of the regulatory protein system associated with a particular cell type? (2) Is there a particular association of each of the polymorphic forms of the regulatory protein, that is, are the regulatory proteins laid down as a 'kit' in a given muscle cell?

The localisation of the polymorphic forms of regulatory proteins has been determined in individual cells by staining serial cross sections of skeletal muscle by the immunoperoxidase technique with antibodies to each of the purified proteins in turn. As the polymorphic forms of troponin I, troponin T, troponin C and tropomyosin are single polypeptide chains and therefore presumably single gene products, specific antibodies prepared against each of them can be used to identify unambiguously the form of each protein present in a given cell. Such studies with the regulatory proteins therefore have advantages over similar studies with myosin, each polymorphic form of which is the product of at least three structural genes. For this reason localisation studies using antibodies prepared against the whole myosin molecule, part of the molecule or one of its polypeptide subunits may not provide unambiguous information about the nature of the whole myosin molecule in the cell. This may explain why some groups report that slow myosin is present in developing skeletal muscle^{26,27} whereas other investigators conclude that the fast skeletal myosin is the major form in this tissue (ref. 27 and N. Rubinstein, personal communication). There are still other reports suggesting that myosin present in fetal muscle differs from the fast and slow forms of adult muscle^{30,31}.

Preparation and specificities of the antibodies

The fast and slow skeletal muscle forms of troponin I were isolated from rabbit white and red skeletal muscle as described by Dhoot *et al.*³² and the corresponding polymorphs of troponin T isolated from the same sources by the methods of Perry and Cole¹³ and Margossian and Cohen³³. Troponin C was isolated from combined chicken breast and leg muscles by the method of Perry and Cole¹³. All proteins were examined for homogeneity by electrophoresis of 20–30 μ g on polyacrylamide gels in 0.1% SDS, 85 mM-Tris, 400 mM borate buffer, pH 7.0. Only preparations that migrated as a single band were used as antigens. The purity of the two forms of troponin I was confirmed by comparing the mobilities of the complexes formed by the polymorphs with rabbit fast skeletal muscle troponin C^{10,32}. Although isolated from mixed breast and leg muscles of the chicken, troponin C behaved as a single antigen and its antibody does not react with the cardiac form of the protein³⁴. Further evidence for its homogeneity is given by the fact that no heterogeneity has been observed in sequence studies of chicken skeletal troponin C prepared from the same source³⁵.

Antibodies to the different forms of each of the regulatory proteins of skeletal muscle of the rabbit were raised in guinea pigs in the manner described elsewhere for antibodies to troponin I^{24,32}. The specificities of the antibodies in all cases were established by the Ouchterlony immunodiffusion test³², by the demonstration of specific staining of isolated myofibrils and by

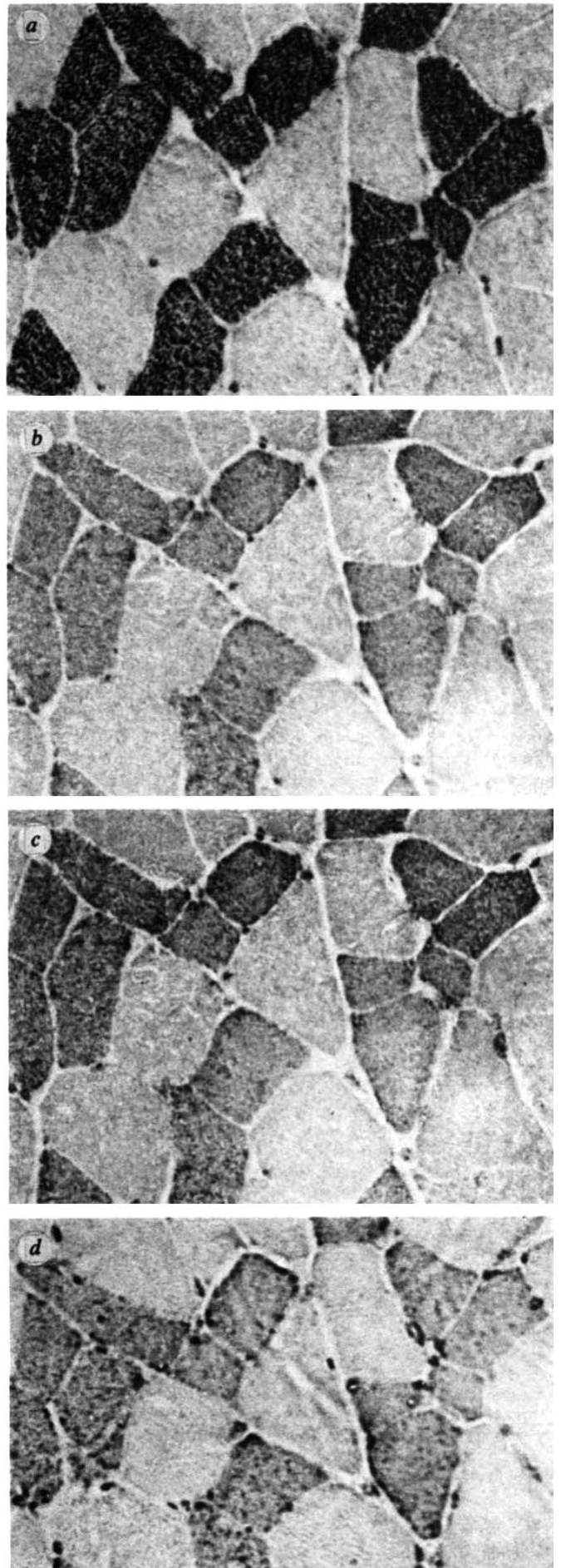


Fig. 2 Serial sections of human semispinalis capitis muscle stained for the troponin components and α -tropomyosin. Sections were stained by the indirect immunoperoxidase staining technique as described in the legend to Fig. 1. *a*, Fast skeletal troponin I; *b*, fast skeletal troponin T; *c*, fast skeletal troponin C; *d*, α -tropomyosin; $\times 200$.

the use of adsorption techniques involving antigen linked to Sepharose or cellulose carbonate³⁶. The specificity of each antibody was further confirmed by the staining of muscle sections using the immunoperoxidase technique³². If the antibody was specific for a single polymorphic form only one fibre type was stained (Fig. 1c, d and Fig. 2). If it also contained antibody to the other form, all cells in a section of adult skeletal muscle were stained.

Although usually specific for the polymorphic form of the protein used as antigen, the antibodies to the myofibrillar regulatory proteins are not species specific^{22,32,34}. The only exception reported to date is the antibody to rabbit β -tropomyosin raised in the guinea pig. This antiserum seemed to be specific for rabbit β -tropomyosin as judged by immunodiffusion²².

Cell types and the different forms of the troponin components and tropomyosin

Immunoperoxidase studies in muscle cross-sections showed that fast skeletal troponin I was localised in type II cells (those staining dark for myosin ATPase measured at pH 9.4 (ref. 1) and slow skeletal troponin I in type I cells (those staining dark for myosin ATPase measured after preincubation at pH 4.2 (Fig. 1a, b). This localisation was a feature of all muscles from the human, rabbit, rat, mouse, hamster, rhesus monkey and baboon that were examined³². In normal adult muscle, virtually all the cells studied appeared to contain either one or other of the two forms of skeletal troponin I. In Fig. 1c, d this distribution is illustrated for mouse gastrocnemius muscle. Only on very rare occasions were intermediate type cells seen that stained for both fast and slow forms of troponin I. In these cases the intensity of staining for each polymorphic form of skeletal troponin I was less than that observed in cells that stained for one form only.

In view of the precise and clear differentiation of adult skeletal muscle cells into two types based on the immunoperoxidase staining method for fast and slow skeletal muscle forms of troponin I, we have suggested that this procedure presents a rapid, convenient new method for typing muscle cells³².

Study of serial sections showed that the antibodies to the fast skeletal muscle forms of troponin T, troponin C and α -tropomyosin stained the same cells as those stained by fast skeletal muscle troponin I. This distribution is demonstrated with human semispinalis capitis muscle in Fig. 2, but has been observed in all muscles studied to date. As far as it could be judged from the intensity of staining observed in the immunoperoxidase test, the fast skeletal muscle forms of the components of the troponin complex and α -tropomyosin were absent from the type I cells. Slow skeletal muscle troponin T was localised in the type I cells. The specificities of the antibodies to the fast and slow forms of troponin T and the differential staining of the type I and type II cells with those antibodies is the first unambiguous demonstration that the slow and fast skeletal muscle forms of troponin T are different. Preliminary studies with antibody raised against rabbit cardiac troponin C indicate that this antibody reacts with type I cells only. In Ouchterlony diffusion tests the antibody gave a precipitin line with troponin C isolated from rabbit slow skeletal and cardiac muscles but not with fast skeletal muscle troponin C. Our results do not permit us to decide whether troponin C in the type I cells is identical with cardiac troponin C or merely cross-reacts with antibody to this protein. The primary sequences of troponin C from rabbit slow skeletal muscle and bovine cardiac muscle are very similar (J. M. Wilkinson, personal communication).

Extrapolation from the general pattern of results obtained with antibody to α -tropomyosin and the fact that all the muscles studied contain β -tropomyosin suggest that the latter polymorph is located in type I cells in mammalian muscle. Preliminary studies with antibody to β -tropomyosin indicate that this is the case (G. K. D., N. Frearson and S. V. P., unpublished

results). Our data do not yet permit us to conclude with certainty whether β -tropomyosin is absent or present in type II cells. As the results indicate that α -tropomyosin is absent, or present in such small amounts that it cannot be identified by the immunoperoxidase technique in type I cells, tropomyosin must be present as the β_2 dimer in these cells. Direct evidence for the

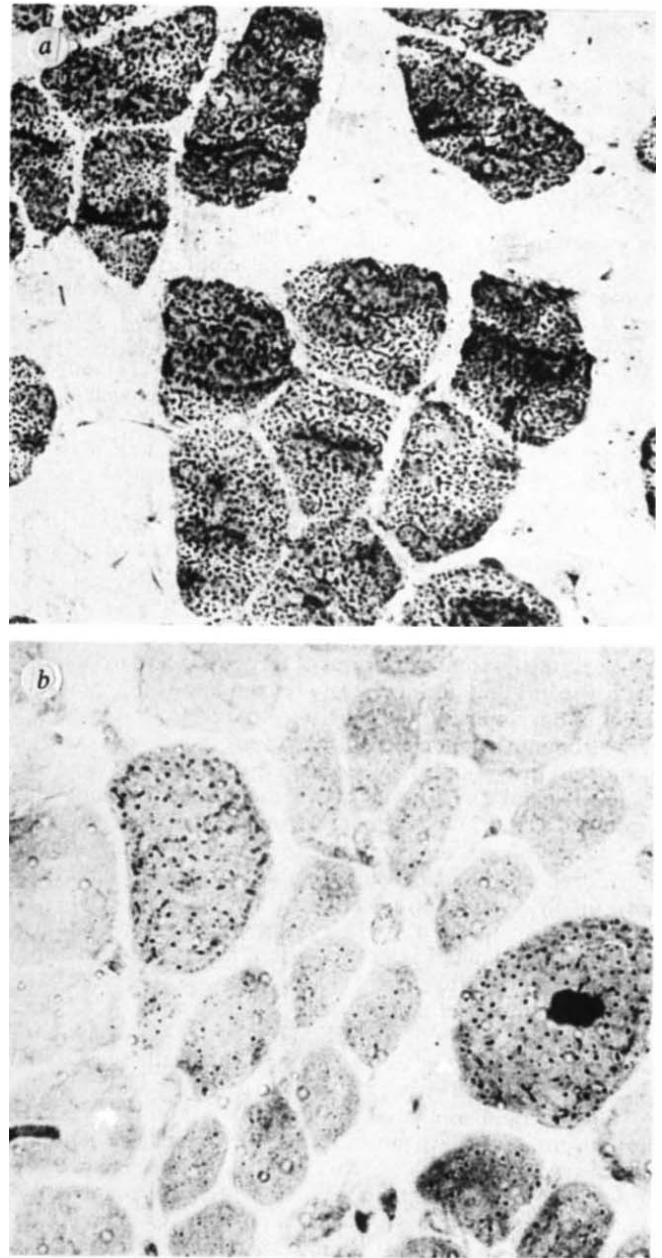


Fig. 3 Comparison of localisation of fast skeletal troponin I in normal and dystrophic human muscle. Sections stained for fast skeletal troponin I by the indirect immunoperoxidase technique as described in Fig. 1. a, Normal human quadriceps muscle; b, quadriceps muscle from a patient with Duchenne muscular dystrophy; $\times 200$.

existence of the β_2 form of tropomyosin in adult muscle has not previously been obtained, although it must exist in rabbit fetal muscle, the tropomyosin of which consists of 80% of the β form⁴¹. Table 1 summarises the conclusions we can make so far on the localisation of the polymorphic forms of the regulatory proteins in the two types of adult skeletal muscle.

Factors affecting the expression of genes controlling synthesis of regulatory proteins

Our studies suggest that there is a very precise association of the different polymorphic forms of the regulatory proteins in normal adult skeletal muscle. The existence of two isoenzymic forms of fast and slow myosin in type II and type I cells respectively, however, indicates that there may be more flexibility as to the form of the myosin molecule incorporated into the myofibrillar structure of a given fibre type than there is with the regulatory proteins. Such a rigid association of the different forms of the regulatory proteins in adult skeletal muscle must be an important factor in determining the contractile properties of the myofibril that are characteristic for the cell type.

The presence of a single polymorphic form of each of the regulatory proteins in a given cell type is a feature of adult muscle. This does not apply at all stages of muscle development for we have observed fast and slow forms of troponin I, troponin T and troponin C in the same cells in developing rabbit, rat and mouse leg muscles. Gauthier *et al.*²⁷ and N. Rubinstein (personal communication) have reported the fast and slow forms of myosin to be present in a single cell in developing muscle, as have Pette and Schnez⁵ in adult muscle after direct stimulation with frequencies different from that normally associated with the muscle.

In newborn animals all the cells from skeletal muscle of the leg stain for fast troponin I. A few, which are presumptive type I fibres, stain weakly for slow troponin I and as development proceeds those cells containing slow troponin I progressively stain more strongly for the slow polymorph and less strongly for the fast form (Fig. 1e, f). Finally the latter disappears completely and the cells appear as normal type I cells staining only for the slow forms of troponin I. A similar pattern of localisation is shown by the fast and slow forms of troponin T and troponin C. Thus it seems that during the late fetal and the early postnatal stages of development, the genes responsible for the fast forms of the troponin components are active in all muscle cells. Only in those cells programmed to become type I fibres are the genes responsible for the slow forms of the troponin components expressed as well. As development and specialisation progress, all but one of the genes responsible for the syntheses of the polymorphic forms of a given regulatory protein are suppressed until finally a predetermined kit of myofibrillar protein (see Table 1) is synthesised, probably under some type of control involving coordinated gene expression, possibly similar to the operon type of control observed in prokaryotes. The elucidation of the mechanisms of the control of the expression of the genes responsible for synthesis of the different forms of the myofibrillar proteins presents a fascinating problem of cell specialisation in response to innervation and activity pattern.

Thus the rigid control of the synthesis of the various polymorphic forms of the myofibrillar proteins is a feature of normal adult muscle. Any change from the normal function of the muscle caused by an alteration in the pattern of stimulation or changes induced by cross re-innervation or by regeneration as a result of disease or injury would, therefore, be expected to change the pattern of localisation of regulatory proteins and possibly also other myofibrillar proteins. It was mentioned above that fibres from the skeletal muscle of adult animals which stained for both fast and slow forms of skeletal troponin I were observed very infrequently. These cases could be explained on the basis that the muscle was not normal or that the animal had been treated in some way that could have promoted some change in its muscle. This view has been reinforced by the fact that examination of samples of muscles from patients with some known primary and secondary myopathies has usually shown that a large number of cells contain both fast and slow polymorphic forms of troponin I and troponin T. This is illustrated for troponin I in Fig. 3 which shows sections through muscle from a normal adult and a patient suffering from Duchenne muscular dystrophy. The study of the distribution of the different forms of the regulatory and probably other myofibrillar

Table 1 Distribution of polymorphic forms of the myofibrillar proteins in skeletal and cardiac muscle of mammals

	Skeletal		Cardiac
	Type I	Type II	
Myosin	Slow A1 Slow A2 ²	Fast A1 Fast A2 ^{2,3}	Cardiac
Actin	α ⁴⁰	?	Cardiac ⁴¹
Tropomyosin	β	α	α †
Troponin C	Slow (= cardiac?) [*]	Fast	Cardiac
Troponin I	Slow	Fast	Cardiac
Troponin T	Slow	Fast	Cardiac

^{*} Only type I fibres stained when sections were treated with anti-cardiac troponin C serum. The primary sequences of troponin C from rabbit slow skeletal muscle and bovine heart are very similar (J. M. Wilkinson, personal communication).

† Although the α -tropomyosin present in cardiac muscle is very similar to the α form present in skeletal muscle it will be necessary to determine the primary sequence to establish whether the identity is complete.

proteins in muscle cells shows considerable promise for the diagnosis and study of the origin of human muscle disease.

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SS433—a massive black hole?

SPECTROPHOTOMETRIC observations by Margon *et al.*¹ have drawn attention to some remarkable spectroscopic activity in the object Stephenson–Sanduleak 433. In addition to broad, intense Balmer, He I and He II emission lines, Margon *et al.*¹ report the presence of broad, strong anomalous emission lines which move rapidly across the spectrum. For example, their Fig. 3 shows the behaviour of two such lines (one at $\sim 6,000 \text{ \AA}$ and the other at $\sim 7,400 \text{ \AA}$ with mean value just redwards of $H\alpha$) on three nights in a four-day interval. The IR line moved redwards by $\sim 150 \text{ \AA}$ and the red line bluewards by $\sim 70 \text{ \AA}$. If interpreted as Doppler shifts these movements imply velocity changes of $6,000 \text{ km s}^{-1}$ and $-3,500 \text{ km s}^{-1}$ respectively. We propose here that these anomalous emission lines are produced by an emitting ring of gas in a circular orbit around a central, massive black hole.

The line profile of emission from such an orbiting ring (see ref. 2) consists of two emission peaks, one on either side of the rest wavelength λ_0 , at wavelengths $\lambda_{\pm}$ corresponding roughly to $\pm V_{\text{orb}}$, the orbital velocity of the ring. That is, roughly, $\lambda_{\pm} \approx \lambda_0 (1 \pm V_{\text{orb}}/c)$. There is also a certain amount of emission between the two peaks, which in this case, we suggest, is masked by the underlying continuum. For SS433, however, the orbital velocity must be so high ($V_{\text{orb}}/c \approx 0.15$) that the orbit is sufficiently close to the central object that the net gravitational redshift of the orbit must also be taken into account. This has the effect of shifting the mean wavelength of the two emission peaks to the red of the rest wavelength as is indeed observed.

For a thin ring in a circular orbit at radius $R = r GM/c^2$ around a Schwarzschild black hole of mass M , the two emission peaks will be at wavelengths given roughly by

$$\lambda_{\pm} = \lambda_0 \left\{ 1 \pm \left(1 - \frac{2}{r} \right)^{-1/2} \frac{\sin i}{r^{1/2}} \right\} / \left(1 - \frac{3}{r} \right)^{1/2}$$

where i is the inclination of the ring's orbit to the line of sight³. These wavelengths are shown for $H\alpha$ and $H\beta$ in Fig. 1, for various values of r and i . Also shown are the wavelengths observed by Margon *et al.*¹, which can be fitted by a ring of given inclination whose radius steadily decreases with time. Note also that as the ring's radius decreases, we would expect the blueward peak to reverse direction, having got as far as the region around He I at $5,876 \text{ \AA}$, the precise value depending sensitively on the inclination (see ref. 4). At the same time the red peak from $H\beta$ appears in the same region. Evidence for such behaviour is reported by Ciatti *et al.*⁵ and by Margon *et al.*¹. Furthermore, from symmetry considerations we would expect the profiles of the emission peaks at any given time to be mirror images of each other (at least on timescales longer than the orbital time). The data presented by Margon *et al.* lend some credence to this. Although we have considered mainly the strong Balmer lines, there is evidence that other lines (such as, He I, He II) display similar behaviour.

We now consider the physical properties of the emitting region. The width of the emission peaks indicates that the thickness of the ring, ΔR , is small, say $\Delta R \leq 0.1R$. Taking $R \approx 50 GM/c^2$ (see Fig. 1) we find that for the emitting region to be large enough that its brightness temperature in the lines does not exceed $\sim 10^4 \text{ K}$, we require $M \geq 3 \times 10^5 M_{\odot}$. Hence we conclude that the central object is a massive black hole. To obtain the observed (dereddened) anomalous line luminosity, we find that the particle density in the emitting region is $n_{\text{em}} \sim$

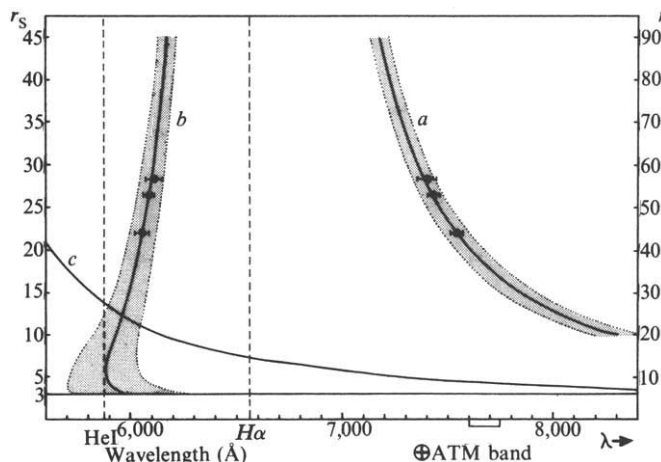


Fig. 1 The predicted wavelengths λ of the red (a) and blue (b) wings of $H\alpha$ and the red (c) wing of $H\beta$ are shown as functions of the radius of the emitting ring, r in mass units or r_s in Schwarzschild radius units, for inclination $i = 45^\circ$. The shaded region corresponds to $40^\circ \leq i \leq 50^\circ$. The filled circles and bars indicate the positions and widths of the lines observed by Margon *et al.* on 23, 24 and 26 October 1978. Thus the observations are consistent with a steadily decreasing radius. Also shown are the rest wavelengths of He I, $H\alpha$ and of the atmospheric A band.

10^{12} cm^{-3} and the total emitting mass to be $m_{\text{em}} \sim 10^{24} \text{ g}$. Note that the rate at which such a mass releases energy as it falls from $r = 28$ to $r = 22$ in a time of three days (Fig. 1) is $\sim 10^{36} \text{ erg s}^{-1}$, comparable to the dereddened anomalous emission line luminosity.

Ipsier and Price⁶ have considered accretion on to massive black holes within the galaxy. They find that a hole of $\sim 3 \times 10^5 M_{\odot}$ passing through the plane of the galaxy would accrete sufficiently to radiate a total luminosity of $\geq 10^{38} \text{ erg s}^{-1}$. They also predict that, if a large part of the mass of our galaxy is in the form of such objects, the nearest such object should be at a distance of a few kpc and have a velocity of $\sim 300 \text{ km s}^{-1}$. These findings are in accord with the observations of SS433. We suggest therefore that the optical continuum radiation, broad emission lines, weak radio and X-ray emission from SS433 are produced by the accretion process.

One problem with our model is the explanation of why the emitting ring remains so narrow. The effect of viscosity on an accreting ring spreads the ring out as it accretes⁷. The emission observed may come predominantly from the densest part of the accreting ring; or we may be witnessing the accretion of a solid body of about planet size (say of mass $\sim 10^{28} \text{ g}$) as it spirals inwards because of friction within a more slowly moving accretion disk. The anomalous emission would then come from a thin ring of steadily decreasing radius in the neighbourhood of the planetoid. In this case the orbital period of $\sim 1 \text{ h}$ might be detectable.

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R. J. TERLEVICH
J. E. PRINGLE

*Institute of Astronomy,
Madingley Road,
Cambridge, UK*

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Neutrinos from neutron stars

SEVERAL schemes to detect ultra-high energy (UHE: $\geq 10^{12}$ eV) muons and neutrinos produced by cosmic ray interactions in the atmosphere have been recently studied¹, and the applicability of the resulting designs to extraterrestrial sources is being discussed². We present here the results of a calculation to determine the flux of UHE neutrinos from galactic neutron stars and the consequent number of point sources detectable at the sensitivity threshold of the proposed deep underwater muon and neutrino detector¹ (DUMAND) array.

Pulsars, with their huge magnetic and electric fields and their ready supply of (rotational) energy, are obvious candidates as sources of UHE particles and radiation³. The Crab pulsar emits pulsed γ -rays at energies exceeding 10^{12} eV, and the neutron star in the binary X-ray system Cyg X-3 has been detected as a UHE γ -ray source modulated at its binary orbital period of 4.8 h (ref. 4). In addition, pulsars are considered to be a likely site of cosmic-ray particle acceleration, and the highly relativistic wind from young sources probably dominates the energetics of some supernova remnants.

The requirements for the production of celestial UHE neutrinos are simply a source of UHE particles, and sufficient target material to produce a significant probability that these particles will convert their energy into neutrinos by a kaon/pion-producing collision followed by the charged meson's decay. For example, to convert $\sim 50\%$ of its energy into neutrinos, a 10^{12} eV proton must traverse $\geq 50 \text{ g cm}^{-2}$ of material or a column density of $\sim 10^{28}$ high energy photons cm^{-2} (ref. 3). The high photon densities are probably not relevant to neutron stars in a galactic setting and will not be considered further here. Table 1 lists common pulsar environments and the resulting column densities of matter encountered by a UHE proton on its journey from the neutron star's surface to Earth. In general, for single pulsars, it seems that the amount of material present is 3–5 orders of magnitude too small; even for a source on the far side of the Galaxy with a line of sight passing through several giant molecular clouds, $<1\%$ of the material needed by a proton for the deposition of half its energy in neutrinos is encountered.

Only in the case of a neutron star in a close binary system with a companion undergoing rapid mass loss does the amount of matter become significant. In systems where massive accretion disks or circumstellar shells develop, or where the neutron star actually buries itself within the envelope of its companion⁵, the

Table 1 Location of the target material

Location	Density (cm^{-3})	Path length (pc)	Amount (g cm^{-2})
Supernova remnants (such as Crab Nebula)	10	1	10^{-4}
General interstellar medium	1	5000	10^{-2}
Giant molecular clouds			
(a) Core	10^6	0.1	10^{-1}
(b) Halo	10^3	10	10^{-2}
Binary star systems with semi-major axes $R \sim 10 R_\odot$ and mass loss rates $\dot{M}$ of:			
(a) $\dot{M} = 10^{-6} M_\odot \text{ yr}^{-1}$	3×10^{11}	10^{-5}	3
(b) $\dot{M} = 10^{-9} M_\odot \text{ yr}^{-1}$	3×10^8	10^{-5}	3×10^{-3}

Table 2 Pulsar energy loss rates

Pulsar age (yr)	No. observed with $\tau \leq 10^6 \text{ yr}$	$\dot{E}$ ($10^{34} \text{ erg s}^{-1}$)	Estimated number in Galaxy	
			Isolated	In accreting binaries
$0-1.0 \times 10^3$	1	47,000	150	1
$1.0 \times 10^4 - 5.0 \times 10^4$	2	400	7,000	7
$5.0 \times 10^4 - 1.0 \times 10^5$	3	2.7	7,500	7
$1.0 \times 10^5 - 3.3 \times 10^5$	7	3.0	35,000	35
$3.3 \times 10^5 - 6.7 \times 10^5$	9	1.3	50,000	50
$6.7 \times 10^5 - 1.0 \times 10^6$	3	0.5	50,000	50
Total	25		$\sim 150,000$	150

column densities can easily exceed the required 50 g cm^{-2} . In the estimates of neutrino fluxes derived below, we adopt a conversion efficiency $\eta_T = 10^{-1}$ for the energy available in UHE particles from neutron stars in such binaries, and $\eta_T = 10^{-4}$ for the remaining objects.

The ultimate power source for relativistic particles and radiation from neutron stars is their rotational kinetic energy. All of the radio pulsars for which measurements have been made are observed to be slowing down. Their energy loss rate $\dot{E}$ is given by

$$\dot{E} = \frac{1}{(2\pi)^2} I \nu \dot{\nu} = 4 \times 10^{46} \nu \dot{\nu} \text{ erg s}^{-1}$$

where ν and $\dot{\nu}$ are the pulsar rotation frequency and its first derivative, and the value of the star's moment of inertia I is taken to be 10^{45} g cm^2 . The potential UHE particle luminosity (L_p) from the Crab pulsar, then, is $\sim 5 \times 10^{38} \text{ erg s}^{-1}$, while from a typical 1 Myr old source, L_p is $\sim 5 \times 10^{33} \text{ erg s}^{-1}$ (see Table 2); these numbers represent an absolute, model-independent upper limit to the energy available in UHE particles from pulsars.

Michel⁶ offers an alternative to this naive assumption of a rotational energy-to-particle conversion efficiency of unity. Working from the basic assumption that the plasma being accelerated from the neutron star's polar cap is described as space charge limited flow, he has performed a dimensionless analysis which indicates that most of the star's energy loss goes into electromagnetic fields rather than particles, regardless of the physical parameters of the source. In particular, one can estimate L_p and the average particle energy ϵ_p solely as a function of the observed energy loss rate and the charge and mass of the accelerated nuclei. The particle energies are just those required for UHE neutrino production: for the range $10^{32} \leq \dot{E} \leq 10^{39}$, we obtain $2.5 \times 10^{12} \text{ eV} \leq \epsilon_p \leq 1.5 \times 10^{14} \text{ eV}$ for iron nuclei and values a factor of 2–4 less for α particles. However, the conversion efficiency for rotational energy to particles, η_E , is typically $\leq 1\%$; we find

$$L_p = 6 \times 10^{35} (\dot{E} \times 10^{-38})^{3/4} \text{ erg s}^{-1}$$

implying a Crab pulsar particle luminosity of $L_p \sim 2.4 \times 10^{36} \text{ erg s}^{-1}$ (for iron ions) which decreases to $L_p \sim 5 \times 10^{32} \text{ erg s}^{-1}$ for a 1 Myr old source (these values are lower by a factor of ~ 4 for α particles). For those neutron stars in accreting binaries, the infalling plasma may hinder the particle acceleration mechanism and reduce the UHE particle flux still further.

Having obtained estimates of the relevant efficiencies for the energy transformation rotational kinetic $\rightarrow$ relativistic particle $\rightarrow$ UHE neutrino, we need only determine the number of active neutron stars in the Galaxy to establish limits on the number of detectable neutrino sources. X-ray catalogues^{7,8} (which are complete for the galactic sources with luminosities $\geq 10^{36} \text{ erg s}^{-1}$) list ~ 100 objects thought to contain heavily accreting neutron stars in binaries (type (a) binary of Table 1), while a review of data on X-ray transients⁹ suggests perhaps 10–50 times this number of systems may exist with lower and/or sporadic accretion rates. Many authors^{10–14} have analysed the

Table 3 Neutrino luminosities and the number of detectable sources*

$\dot{E}$ (erg s ⁻¹)	Isolated stars ($\eta_T = 10^{-4}$)				Close binary systems ($\eta_T = 10^{-1}$)			
	$\eta_E = 1^\dagger$		$\eta_E = \text{SCLF}^\ddagger$		$\eta_E = 1^\dagger$		$\eta_E = \text{SCLF}^\ddagger$	
	L_ν (10 ³⁰ erg s ⁻¹)	No. detectable	L_ν (10 ³⁰ erg s ⁻¹)	No. detectable	L_ν (10 ³⁰ erg s ⁻¹)	No. detectable	L_ν (10 ³⁰ erg s ⁻¹)	No. detectable
10 ³⁸	10 ⁴	1	60	0	10 ⁷	1	60,000	0.2
10 ³⁶	10 ²	1	2	0	10 ⁵	0.5	2,000	0.1
10 ³⁴	1	0.1	0.06	0	10 ³	0	60	0
10 ³²	10 ⁻²	0	0.002	0	10	0	2	0

* Assuming a DUMAND sensitivity threshold of 10^2 eV (cm² s)⁻¹. Note that no sources are detectable at the threshold of current detectors of 10^5 eV (cm² s)⁻¹.

† Model independent upper limits.

‡ Based on the space charge limited flow (SCLF) assumption of Michel⁶.

available pulsar data and have estimated the total number of active radio pulsars in the Galaxy to be between 10^5 and 10^6 . However, due to their monotonic decrease in energy loss rate, only the youngest of these pulsars will contribute significantly to the flux of UHE particles available for neutrino production. Although it is generally accepted that pulsar characteristic ages ($\tau = P/2\dot{P}$) are poor indicators of the true source ages^{10,11,15}, the values of τ for the two youngest objects (the pulsars associated with the Crab and Vela supernova remnants) agree well with the independent age estimates available, and most authors agree that up to about 1×10^6 y, τ may provide a reasonable chronological age. Of the ~ 110 sources with measured period derivatives, 25 have characteristic ages of < 1 Myr^{16,17}. The numbers of these pulsars in each of several age brackets, their observed energy loss rates and the extrapolated total population of each group in the Galaxy, are shown in Table 2. The estimates for single pulsars are based on a steady-state birthrate of one source per 6 yr^{10,14}. The numbers for neutron stars in binary systems are crude estimates based on a constant (with age) fraction of 0.1% of the total population. This value is consistent with the X-ray data, but it does not include evolutionary considerations which might either selectively enhance (such as, by the production of relativistic wind-induced envelopes around young objects¹⁸) or deplete (for example, due to long evolutionary time required for the companion to reach the mass-losing stage¹⁹) the number of young objects in accreting systems.

The proposed DUMAND array¹ has a point source detection threshold of $\sim 10^2$ eV cm⁻² s⁻¹. The results presented in Tables 1 and 2, with our adopted efficiencies η_T and η_E , allow us to estimate the number of neutron stars that we can expect to observe at this level of sensitivity. We assume that the young pulsars enumerated in Table 2 are uniformly distributed throughout the galactic disk within a galactocentric radius of 12 kpc (this ignores the radial and Z-height dependences of the pulsar distribution¹⁰, however, this will not appreciably affect the results). Table 3 presents the neutrino luminosities for various energy loss rates and the estimated number of detectable sources based on our derivations of η_E and η_T . To typical astrophysical accuracy, we may conclude that there will be no source confusion problem for DUMAND (resolution $\leq 1^\circ$) in observing galactic neutron stars, but, with a little luck, a few detections are possible.

Note that any such source observed in the UHE neutrinos will not be invisible to all other types of detectors. These objects will produce a copious flux of γ rays, and in the case of the close binary systems, an accretion-powered X-ray source is also expected. In fact, among the 15 or so localised 100 MeV γ -ray sources in the galactic plane²⁰, five are associated with known or suspected neutron stars: four radio pulsars including the one in the Crab Nebula, and the binary X-ray source Cyg X-3. The latter two objects have already been observed by Cerenkov detectors in the UHE regime ($E_\gamma \geq 10^{12}$ eV)⁴. In the case of the radio pulsars, these high energy photons may be produced through curvature radiation or some other processes associated with the pulsar mechanism rather than through the meson decay

which would require an accompanying flux of neutrinos. However, the case of Cyg X-3 is promising. Bignami, Maraschi and Treves²¹ and others^{22,23} have suggested a model for this source involving a young neutron star embedded in the dense stellar wind of its red dwarf companion. The X-ray emission is powered not by accretion, but by interaction of the relativistic outflow (in dipole radiation, particles, and so on) from the pulsar with the plasma surrounding the system. The observed UHE γ -rays show an orbital phase distribution which peaks when the X-ray source (the neutron star) is near eclipse⁴; that is, when our line of sight passes through the maximum path length of circumstellar target material. No other similar systems have been optically identified, and it is difficult to resist the speculation that this source is one of the handful of binary neutrino sources predicted in Table 3.

We have attempted to estimate the number of neutrino point sources powered by galactic neutron stars which will be detectable with the DUMAND array. While the prospects for such observations are far from sanguine, the totally new view of the objects discussed here offered by a UHE neutrino telescope can only add to the many potentially fundamental physical insights that the study of galactic neutron stars is sure to provide.

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DAVID J. HELFAND

Columbia Astrophysics Laboratory,
Departments of Astronomy and Physics,
Columbia University,
538 West 120th Street,
New York, New York 10027

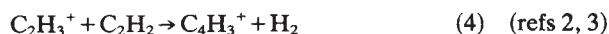
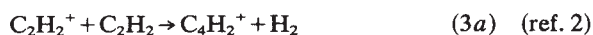
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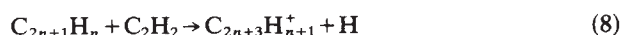
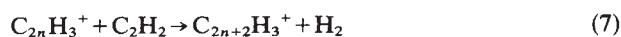
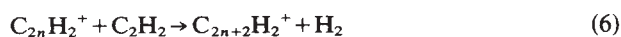
Long chain carbon molecules and diffuse interstellar lines

THE diffuse interstellar lines, seen in the optical spectra of stars which lie behind fairly low density interstellar clouds, have remained unidentified for many years. It has recently been suggested¹ that the diffuse interstellar lines are the absorption bands of long chain carbon molecules, C_n , where n may be in the range 5–15. As one possible source for these molecules, Douglas¹ proposes that long chain hydrocarbons are synthesised in dense interstellar clouds. After cloud disruption, the hydrocarbons may lose their hydrogen atoms by photodissociation and exist as pure carbon chains. While the shortest of the chains (C_2 , C_3 , C_4) will themselves be photodissociated, Douglas¹ argues that chains beyond a certain length are stable against photodissociation and will persist in the low density clouds in which the diffuse interstellar lines are formed. As a first step in evaluating the feasibility of this route, we estimate here the abundances of chain hydrocarbon molecules which would be expected in dense interstellar clouds as a result of gas-phase chemistry alone. The rather high abundances of hydrocarbons which we predict support the identification of carbon chains as the source of the diffuse interstellar spectral features.

Rate coefficients for ion–molecule reactions leading to hydrocarbon-chain molecules with up to five carbon atoms have been measured in the laboratory^{2,3}. The most important of these measured reactions are



Further acetylene additions can occur by reactions of the form³



for $n = 2, 3, 4, \dots$

We have argued⁴ that methane, which is required if the synthetic reactions (1–5) are to proceed, should be abundant in dense clouds. We found, for a fractional ionisation of $e/n = 3 \times 10^{-8}$ (refs 5, 6), and a rate coefficient of $4 \times 10^{-13} \text{ cm}^3 \text{ s}^{-1}$ for the radiative association reaction of CH_3^+ with H_2 (ref. 7), that $[CH_4]/n \approx 10^{-6}$, where $n \equiv n(H) + 2n(H_2)$. The recent detection of methane in Orion A⁸, although not leading to a reliable column density because of non-thermal excitation, is compatible with a high methane abundance. Acetylene is produced by reaction (1a) and is destroyed by reaction (2) so that the relative abundance of acetylene is

$$C_2H_2/n \approx \frac{k_{1a}(C^+/n)(CH_4/n)}{k_2(C^+/n)}$$

where we use the notation $X/n \equiv [X]/n$. Since $k_{1a} \approx k_2$, we find that $C_2H_2/n \approx CH_4/n (\approx 10^{-6})$.

At each step in the sequence of reactions (1–8), recombination with electrons leads to neutral hydrocarbons. The destruction rate of the neutral molecule is required for a determination of its abundance. The assumption that destruction is by reaction with C^+ provides an estimate of the actual destruction

rate for a complex molecule⁴. With this assumption, the equilibrium abundances of the neutral molecules are readily obtained. In view of the uncertainty in the number of hydrogen atoms ejected after recombination, we use the notation C_nH_m for the neutral molecule containing n carbon atoms. For example, C_4H_m will represent all of the likely products for the recombination of both $C_4H_3^+$ and $C_4H_2^+$, namely C_4 , C_4H , C_4H_2 and C_4H_3 .

To illustrate the method of calculation we will obtain the equilibrium abundances of C_3H_m and C_5H_m . C_3H_m is formed by reaction (2) followed by recombination, and is destroyed by reactions with C^+ (by assumption), so that

$$C_3H_m/n = \frac{k_2(C^+/n)(C_2H_2/n)}{k_{C^+}(C^+/n)}$$

where k_{C^+} is the rate coefficient of the reaction



If $k_{C^+} \approx k_2$, we find that $C_3H_m/n \approx C_2H_2/n \approx 10^{-6}$. Similarly,

$$C_5H_m/n = \frac{k_5(C_3H^+/n)(C_2H_2/n)}{k_{C^+}(C^+/n)}.$$

Since C_3H^+ is formed by reaction (2) and destroyed by recombination with electrons,

$$C_3H^+/n = \frac{k_2(C^+/n)(C_2H_2/n)}{k_e(e/n)}$$

where $k_e (\approx 3 \times 10^{-7})$ is the recombination rate coefficient. Using $C_2H_2/n \approx 10^{-6}$, $k_{C^+} = 2 \times 10^{-9} \text{ cm}^3 \text{ s}^{-1}$, $e/n = 3 \times 10^{-8}$, and the measured values³ for k_2 and k_5 , we find $C_3H_m/n \approx 2 \times 10^{-7}$.

The equilibrium abundances of molecules with up to 12 carbon atoms, obtained with the assumption that reactions (6–8) have a rate coefficient of $2 \times 10^{-9} \text{ cm}^3 \text{ s}^{-1}$, are given in Table 1. It can be seen from Table 1 that the calculated abundances of C_n molecules remain quite high even for n as large as 11. By way of comparison, a fractional abundance of $10^{-9} \leq CH/n \leq 10^{-8}$ produces the strong observed interstellar lines of CH. The decline in abundance towards larger molecules is slower than might have been expected: $C_{2n+1}H_m/C_{2n+3}H_m \approx 5 \approx C_{2n}H_m/C_{2n+2}H_m$ for $n = 1, 2, 3$ and 4. The predicted ratio for hydrocarbons is close to the observed ratio for cyanopolynes of $HC_{2n}CN/HC_{2n+2}CN \approx 4$ for $n = 1, 2$ and 3 (ref. 9).

The predicted abundances of hydrocarbons with an odd number of carbon atoms are higher than the abundances of hydrocarbons with an even number of carbon atoms (Table 1). This occurs because C_3 hydrocarbons are formed by reaction of C^+ with C_2H_2 while C_4 hydrocarbons are produced by the reaction of $C_2H_2^+$ with C_2H_2 . Since C^+ is more abundant than $C_2H_2^+$, C_3H_m will be more abundant than C_4H_m . Subsequent acetylene additions preserve this relation: that is $C_{2n+1}H_m/n > C_{2n+2}H_m/n$.

The fractional ionisation which we have assumed, $e/n \approx 3 \times 10^{-8}$, is an upper limit deduced from observed abundance ratios of isotopic forms of various molecules. It is unlikely that e/n can be much less than 10^{-8} because the observed abundance of HCO^+ is often $HCO^+/n \leq 10^{-8}$, providing a lower limit to e/n if the regions are electrically neutral. Furthermore, model calculations show that, even with extreme heavy element depletion, the fractional electron abundance remains near 10^{-8} (ref. 10). On the other hand, the fractional ionisation in less

Table 1 Predicted relative abundances of hydrocarbons in dense clouds

$C_3H_m/n \approx 1 \times 10^{-6}$	$C_4H_m/n \approx 8 \times 10^{-8}$
$C_5H_m/n \approx 2 \times 10^{-7}$	$C_6H_m/n \approx 2 \times 10^{-8}$
$C_7H_m/n \approx 3 \times 10^{-8}$	$C_8H_m/n \approx 3 \times 10^{-9}$
$C_9H_m/n \approx 7 \times 10^{-9}$	$C_{10}H_m/n \approx 7 \times 10^{-10}$
$C_{11}H_m/n \approx 1 \times 10^{-9}$	$C_{12}H_m/n \approx 1 \times 10^{-10}$

dense and/or warmer regions may be as high as 3×10^{-7} . A fractional electron abundance of 3×10^{-7} would not change the methane abundance⁴, the acetylene abundance, or the abundance of C_3H_m . All other hydrocarbons, C_n/H_m with $n > 4$, would decrease in abundance by a factor of 10 because their precursor ions, $C_nH_m^+$, would decrease in abundance by this factor.

The high abundances we find here for dense clouds ($\Sigma_{m>5} C_m/n \approx 10^{-7}$) lend support to the idea that C_n molecules may be the source of the diffuse interstellar lines.

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G. F. MITCHELL*
W. T. HUNTRESS JR

Jet Propulsion Laboratory,
California Institute of Technology,
Pasadena, California 91103

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*Permanent address: St. Mary's University, Halifax, Nova Scotia, Canada.

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γ and X rays from the zodiacal dust

γ -RAY lines can be produced by MeV protons in interactions with interstellar^{1–4} and solar coronal matter^{5–7}. Here I show that, in favourable conditions, solar flare protons can produce both observable γ -ray lines and characteristic X-ray lines, when interacting with the material of the zodiacal dust cloud. Of particular interest are narrow γ -ray lines without kinematical broadening ($\Delta E < 1$ keV), which are produced by long-lived

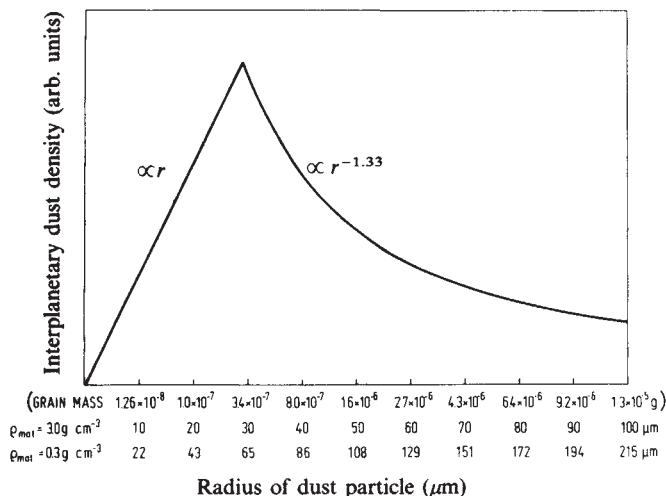


Fig. 1 Idealised mass density as a function of grain size of the zodiacal dust. This was adapted from Giese and Grün's⁶ maximum model. The abscissa shows particle radii for two different assumed grain material densities; also indicated is the corresponding grain mass. This graph shows that the bulk of the zodiacal dust matter is contained in grains with radii $10 \mu\text{m} \leq r \leq 100 \mu\text{m}$.

Table 1 The most intense nuclear γ -ray lines expected from zodiacal dust matter

Element	Photon energy (MeV)	Mean life (10^{-12} s)	4 August 1972 expected line flux at Earth ($10^{-6} \text{ cm}^{-2} \text{ s}^{-1} \text{ sr}^{-1}$)
¹⁶ O	6.23	24.0	1.0
²⁴ Mg	1.37	1.75	1.3
²⁸ Si	1.78	0.68	0.5
⁵⁶ Fe	0.847	9.7	1.2

The line flux expected for the 4 August 1972 event from zodiacal dust oxygen is estimated in the text, the other three values were scaled for differing abundance ratios from ref. 4.

nuclear excited states ($\tau \geq 10^{-12}$ s) in solids. A typical zodiacal dust grain is sufficiently large for such narrow line production, and modern germanium detectors can detect and identify these lines. Observation of X rays and γ rays together would yield information on the average interplanetary dust density, grain size, material density, and chemical composition. This might help to determine whether the dust is of Solar System (for example, cometary) or of interstellar origin. Protons ≥ 10 MeV form a probe for which the dust grains are transparent, so that the measured quantity does not depend on grain size and surface properties, in contrast to the zodiacal light.

The properties of the zodiacal dust are not too well known. The grain size spectrum shows a knee^{8,9} around particle size 3×10^{-7} g, which translates into grain radii (spherical shape assumed) of $r \approx 30 \mu\text{m}$ to $r \approx 60 \mu\text{m}$, for assumed material densities of $\rho_{\text{mat}} = 3 \text{ g cm}^{-3}$ to $\rho_{\text{mat}} = 0.3 \text{ g cm}^{-3}$, respectively. The bulk of the matter is contained in grain sizes between about 10 and 100 μm (see Fig. 1). The range of 10 MeV protons is $\geq 0.1 \text{ g cm}^{-2}$, so the grains are transparent up to $r \approx 1,000 \mu\text{m}$. The total mass density at 1 AU is somewhere between $4 \times 10^{-23} \text{ g cm}^{-3}$ (refs 8, 9) and $4 \times 10^{-22} \text{ g cm}^{-3}$ (refs 10, 11); in the following, ρ is taken as $1.2 \times 10^{-22} \text{ g cm}^{-3}$. The number density dependence on solar distance R is estimated to be $n(R) \propto R^{-\nu}$ with ν between 1.0 and 1.7 (ref. 12). Recent space probe observations imply that ν from 1.3 (ref. 13) to 1.5 (ref. 14). Around the Sun there seems to be a dust-free zone extending to a few solar radii¹⁵. Infrared observations¹⁶ and orbital calculations¹⁷ indicate that the dust cloud indeed extends down to a few solar radii. The chemical composition of the grains seems to be similar to chondrites^{10,18} or even to carbonaceous chondrites^{19,20}. The material density of the dust particles is often assumed to be between that of water and iron²¹, typically $\rho_{\text{mat}} \approx 3 \text{ g cm}^{-3}$. On the other hand, fluffy particles, which consist of a mosaic of smaller particles and which are probably much less dense, have been recorded^{10,20,22,23}. Other estimates are as low as $\rho_{\text{mat}} = 0.18$ (ref. 11).

Nuclei that are excited by 10–20 MeV protons (where the excitation cross-sections exhibit a broad maximum) receive recoil energies in the 10–100 keV/AMU range⁶. Lines from short-lived states or gaseous material would be of the order of 100 keV wide^{2–4,6}. However, in solids such nuclei have projected ranges of several $100 \mu\text{g cm}^{-2}$ (refs 24–26), and their stopping time is of the order of 10^{-12} s, so that lines from longer-lived nuclear states from grains with $r \gg 1 \mu\text{m}$ would have a significant component that is very narrow due to lack of kinematical broadening^{3,4,6}. Table 1 lists the most important long-lived γ -ray lines that can be expected from extraterrestrial matter^{2,4}. These are probably the only lines that will be observable. The carbon 4.44 MeV line is not included because it is short-lived and shows full Doppler broadening in solids, as can be demonstrated in the laboratory²⁷, while the states listed produce a significant narrow component. If the dust were mostly cometary debris, the carbon abundance would be too low to produce an observable line flux anyway.

The expected line flux of the oxygen 6.13 MeV line can be estimated using a grain composition similar to carbonaceous chondrites (see ref. 28), that is $\approx 40\%$ O, $\approx 20\%$ Fe, $\approx 10\%$ Si, $\approx 10\%$ Mg by weight, which for $\rho = 1.2 \times 10^{-22} \text{ g cm}^{-3}$ yields 1.8

O-atoms, 0.26 Fe-atoms, 0.26 Si-atoms, and 0.3 Mg-atoms per cm^3 . This is about 300–1,000 times larger than in the interplanetary gas (see ref. 30).

The emissivity per unit volume is $P_\gamma = \int_0^\infty n \cdot \sigma(E_i, E) \cdot F_p(E) dE \text{ cm}^{-3} \text{ s}^{-1} \text{ sr}^{-1}$, where $n \text{ cm}^{-3}$ is the number density of the nucleus under consideration, $\sigma(E_i, E)$ is the total cross-section for production of a photon of line energy E_i by a proton of energy E , and $F_p(E) \text{ cm}^{-2} \text{ s}^{-1} \text{ sr}^{-1} \text{ MeV}^{-1}$ is the flux of energetic protons. Oxygen cross-sections by Ramaty *et al.*³⁰ are used in an example of the 4 August 1972 particle event with a proton spectrum $F_p(E) = 1.7 \times 10^6 (E/\text{MeV})^{-1.7}$. To determine this spectrum the spectral shape and α/p ratio ($\approx 3\%$) before and after the maximum phase of the event were adapted from ref. 31. Then the maximum phase α -particle flux from ref. 32 was multiplied by 30, because the proton flux measurement suffered from detector saturation. Although the proton flux thus derived is larger than reported elsewhere, it is a realistic estimate because most of the proton detectors in space were probably saturated during the flux maximum. With these values $P_\gamma \approx 7 \times 10^{-20} \text{ cm}^{-3} \text{ s}^{-1} \text{ sr}^{-1}$. Assuming the lateral extent near Earth of this event to be about 1 AU, the total flux at Earth becomes $F_{6.13} \approx 10^{-6} \text{ cm}^{-2} \text{ s}^{-1} \text{ sr}^{-1}$ (see also Table 1). This is about 10–20 times smaller than the sensitivity threshold of currently planned γ -ray detectors in space (aperture of $\approx 1 \text{ sr}$ assumed).

Larger γ -ray fluxes may be observed, for the following reasons: (1) the largest estimates of the dust density are three times the value used here^{10,11}, (2) Conservative extrapolation of particle event statistics³³ indicate the possibility during maximum solar activity of several events per year of the August 1972 size, and ≥ 1 event yr^{-1} of ≥ 10 times that size, occurring all over the visible hemisphere of the Sun. On Earth only those events originating near the preferred solar longitude³³ will be seen as strong particle events, while all events can be seen in γ rays. (3) The detector could view the Sun directly as after the short flash phase of the flare the Sun will be quiet again³⁴, causing no background. Assuming that the proton density (or flux) rises as R^{-2} towards the Sun, and the dust density as $R^{-1.3}$ to $R^{-1.5}$, the γ ray line flux at Earth from the solar direction can be 15–30 times larger than estimated above. Thus, despite the first low estimate above, there is a good chance that these γ -ray lines can be observed in the future.

Protons of this energy also ionise with fairly large probability the K -shells of atoms, while at the same time they generate little continuum X-ray background. The product of proton flux and cross-section peaks at less than 1,000 U_k (where U_k is the K -absorption edge energy), which is as low as 0.5 MeV for oxygen. Grains are not transparent to these protons or to the corresponding K_α -photons. Yet, the characteristic K_α lines should be observable.

K_α line fluxes will be estimated in a way similar to that used for γ -ray line fluxes, the main difference being that the grains are not transparent except for the 6.42 keV K_α line of iron. For simplicity I assume that half the photons that are produced in the outer layer of the grain of thickness $1/(\mu/\rho) \text{ g cm}^{-2}$ leave the grain and can be observed (μ/ρ is the mass absorption coefficient). This 'active' fraction of the total mass of the dust depends on grain material density and composition, and therefore estimates are given for $\rho_{\text{mat}} = 3 \text{ g cm}^{-3}$ and $\rho_{\text{mat}} = 0.3 \text{ g cm}^{-3}$.

Table 2 The most intense K_α lines expected from the zodiacal dust during a solar proton event

Element	K -shell ionisation energy (U_k) keV	K_α -mass absorption coefficient (μ/ρ) $\text{cm}^2 \text{ g}^{-1}$	K_α -line energy keV	4 August 1972 expected K_α -line flux at Earth for grain density	
				$\rho_{\text{mat}} = 3$ g cm^{-3}	$\rho_{\text{mat}} = 0.3$ g cm^{-3}
O	0.53	6.5×10^3	0.52	1.9×10^{-3}	6.6×10^{-3}
Mg	1.31	2.5×10^3	1.26	5.0×10^{-4}	1.5×10^{-3}
Si	1.85	1.3×10^3	1.74	6.8×10^{-4}	1.8×10^{-3}
Fe	7.14	1.0×10^2	6.42	1.5×10^{-3}	1.7×10^{-3}

Fluffy particles probably behave like low density material.

To compute the mass absorption coefficient I have added 20% Ca to the chemical composition assumed above. This should account approximately for the rest of the material which is a mixture of elements ranging from carbon to at least nickel²⁰. I have used experimental and computed mass absorption coefficients^{35,36} and K -shell ionisation cross-sections³⁷, and published quantum yield values³⁸ to derive Table 2. The last two columns of Table 2 contain flux values expected for the 4 August 1972 event.

The main problem for registering these fluxes is caused by the diffuse X-ray background of the sky, which at 6.4 keV is about 0.6 photons $\text{cm}^{-2} \text{ s}^{-1} \text{ sr}^{-1} \text{ keV}^{-1}$ (refs 39, 40). Taking this into account, the expected Fe- K_α flux is about a factor of 3 below the sensitivity threshold of large orbiting X-ray detectors (on HEAO 1). In this case, only a three times larger dust density, or a three times larger particle event would be required for positive detection.

The moon should emit γ -ray lines and X-ray lines by the same mechanisms. In case of the 4 August 1972 event, the oxygen 6.13 MeV line flux at Earth should have been $> 10^{-3}$ photons $\text{cm}^{-2} \text{ s}^{-1}$ (40% O by weight assumed), and the 6.42 keV Fe characteristic X-ray line flux should have been > 0.5 photons $\text{cm}^{-2} \text{ s}^{-1}$ (10% Fe assumed). Proton-stimulated characteristic X-ray emission as compared to X-ray fluorescence from the lunar surface could be of interest to a possible lunar orbiter mission. The solar X-ray spectra are very soft so that not much intensity is expected in energetic fluorescence lines like the 6.4 keV Fe line, while the MeV protons could stimulate these lines in measurable quantities.

Finally, after large solar flare particle events, it is worthwhile to look at γ - and X-ray lines caused by interactions of MeV protons with the zodiacal dust. For MeV protons and γ rays the dust grains are transparent, so that some data can be derived without complicating grain size and surface effects: the mean composition can be derived in a model independent way, and together with *in situ* measurements of the proton flux it can be used to calculate the average spatial density along the line of sight. X-ray observations with some existing knowledge of the grain size distribution and its dependence on solar distance, can be used to give data on the size and material grain density. On the other hand, if the dust properties were sufficiently well known, large particle events could be monitored at other than the preferred heliolongitude.

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WOLFGANG K. H. SCHMIDT

Max-Planck Institut für Aeronomie,
D-3411 Katlenburg-Lindau 3, FRG

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The influence of dynamic loading on sliding friction

THERE have been many studies of the rheology of thin polymeric films in sliding contacts¹⁻⁴, and many of the results have been obtained with a particular experimental arrangement which involves studying the motion of a glass hemisphere traversing a thin film deposited on a smooth glass flat³⁻⁵ (Fig. 1). The development of this subject has concentrated on an important quantity of practical interest, τ , the interfacial shear strength, which may be considered to be the energy dissipated per unit distance per unit contact area. These dissipative processes occurring in a particular film are not generally known. The interfacial shear strength has been found, for a wide range of organic polymers, to depend on many parameters, such as

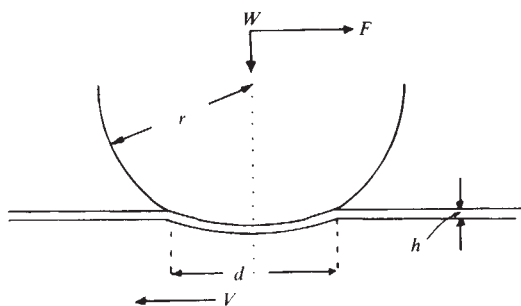


Fig. 1 Schematic diagram of the experimental arrangement. A glass sphere of radius r is loaded against a glass plate on which is deposited a thin organic film of thickness h (typically 100 nm). The surfaces are set in relative motion with a velocity v by the application of frictional force, F , orthogonal to the normal load, W . To a good approximation the area of contact and also the area of film sheared, A , is given by $\pi(WKr)^{2/3}$ where K is $\frac{2}{3}(1-\nu^2)/E$ where E and ν are respectively the Young's modulus and Poisson's ratio of the glass⁶. The contact diameter, d , is $2(A/\pi)^{1/2}$ and the intrinsic contact time, t_c , is d/v . The interfacial shear strength, τ , and mean contact pressure, P_m , are respectively F/A and W/A . The effective rate of strain, $\dot{\epsilon}$, in the film is v/h . Because the mechanical properties of the glasses are invariant with respect to temperature and time, changes in τ in these variables can be attributed wholly to the response of the organic layer. Typically P_m is of the order of 10^8 - 10^9 Pa; $t_c \sim 0.1$ s and $\dot{\epsilon}$ exceeds 10^3 s⁻¹. Classical calculations suggest that adiabatic heating is trivial in these experiments⁷.

contact pressure, temperature and strain rate, for which simple empirical relations have been found⁸. Providing the real area of contact can be estimated, these relationships are of value in predicting the friction of certain lubricated contacts. These relationships are broadly similar to those obtained from the study of the variation of the bulk yield stress of polymers and in certain cases the magnitude of the fitting coefficients (for example, τ_0 and α below) are similar for a given polymer, in bulk and interfacial shear tests. Direct comparison is difficult because interfacial shear measurements generally correspond to much higher pressures and effective strains and rates of strain. However, it seems that τ may be considered a measure of the bulk shear yield or rupture stress of the organic layer in relatively intense deformation conditions. Using a modification of the basic experimental method we have now obtained detailed information on the effect of velocity or contact time on τ .

For the present note it is only necessary to recall that τ is generally an increasing linear function of contact pressure and

$$\tau = \tau_0 + \alpha P_m \quad (1)$$

where τ_0 and α are constants and P_m is the mean effective contact stress (Fig. 1). For organic polymers α is large (0.1-0.6) and for metals and inorganic solids, it is a factor of between 10 and 100 smaller. More recently, further dependent variables have appeared, for example, film preparation conditions⁸ and with reference to this note, contact time, t_c (ref. 9). In this context, the intrinsic contact time is approximately the contact length divided by the sliding velocity (Fig. 1).

Previous studies of the velocity dependence of shear strength for a variety of polymers⁵ showed that generally this quantity increases with velocity or effective rate of strain. The variation of τ seems to be a linear function of $\ln \dot{\epsilon}$ consistent with the response of bulk polymers at lower rates of strain. Although the evidence is not conclusive, it seems that τ_0 , but not α , is an increasing function of $\dot{\epsilon}$. One exception was found, polymethylmethacrylate (PMMA), which when studied at room temperature, showed a decrease. PMMA at 160 °C ($T_g \approx 110$ °C) shows an increase of τ with increasing velocity.

Apart from the generation of an effective strain rate, the nature of such a sliding experiment involves the transient application of a normal stress on the film due to the load in the contact. Thus an infinitely thin element of film (Fig. 1) is subjected to a progressive increase in P up to $3/2 P_m$ followed by a decrease to zero as it leaves the contact. The form of this pressure cycle is given by the hertzian pressure distribution in the contact. It has been hypothesised that the effective (or fictive) contact stress in a viscoelastic material will be somewhat less than that which is applied, due to the inability of the film to respond to the rapid variation during sliding¹. In this way the shear strength may be considered to be attenuated through the pressure term in equation (1), where P_m becomes a fictive pressure and a function of t_c .

Direct experimental confirmation of this hypothesis is difficult, because in practice only small changes in t_c through d can be effected and the variation of v increases $\dot{\epsilon}$. We have introduced a modification to the basic experimental technique which uniquely elucidates the effect of contact time. A periodic loading was superimposed on the hemisphere by means of a steel core coil fed by an a.c. signal resulting in a signal of amplitude about one-tenth of the 'dead' load. In this way a second (extrinsic) contact time is introduced. To compare polymers a loading frequency of 1.5-30 Hz was used. The frictional force responds with a superimposed ripple which may be extracted from dead load friction using a phase-sensitive detector. The ripple amplitude may then be measured as a function of frequency. As a measure of the attenuation of the sinusoidal signal as a function of frequency, a relative attenuation factor, R , was defined as

$$R = \frac{\Delta \text{Ripple amplitude}}{(\text{Ripple amplitude})_{1.5 \text{ Hz}}} \frac{30 \text{ Hz}}{1.5 \text{ Hz}}$$

Table 1 gives values of R for a variety of polymers as well as graphite, MoS₂ and stearic acid for an intrinsic frequency of

Table 1

R	Material
0.45	Molybdenum disulphide
0.45	Stearic acid
0.46	Graphite
0.52	Polyvinyl acetate
0.49	Polycarbonate
0.48	High density polyethylene
0.50	Polystyrene
0.75	Polymethylmethacrylate (room temperature)
0.50	Polymethylmethacrylate (temperature 160 °C)

5 Hz. PMMA at room temperature is the only polymer with high R , confirming that the response of the film is highly contact time sensitive. All other polymers including PMMA at 160 °C show $R = 0.48$ – 0.52 . It thus seems that the dynamic loading technique discerns the influence of contact time and the results are consistent with the velocity behaviour previously obtained. Note that the values of R for non-polymeric solids are slightly lower, indicating that all the polymers studied show some attenuation with contact frequency increase. It would be expected that the non-polymers would not show any retardation in response, and thus $R = 0.45$ seems to be the 'zero' of the technique. Ideally, R should be zero for these films but the apparatus probably has viscous or elastic damping associated with it, although no direct mechanical damping was used.

We have also studied the influence of dynamic contact frequency for a range of intrinsic contact frequencies (generated by maintaining P_m constant and changing v and d). Both the form and magnitude of the attenuation were found to be a function of intrinsic contact frequency. Thus the two loading processes seem to interact for all polymers but the nature of this type of interaction is conceptually difficult to rationalise.

This attenuation of response with contact time decrease has been termed viscoelastic retardation in compression. Previous studies^{10,11} have put forward evidence for its occurrence in oil film shear, although this interpretation was subsequently questioned¹². Recently Johnson and Tevaarwek¹³ found some evidence that was consistent with a delay in response of oil films. They also showed a general similarity in behaviour between thin oil films in elastohydrodynamic contacts and thin polymeric film shear. There is also some evidence that the low strain properties of bulk polymers show some retardation in response following the application of a hydrostatic stress^{14,15}. These data are complicated because of adiabatic heating. In this context it is worth noting that PMMA has a major bulk relaxation (β transition) at ~ 1 Hz at 20 °C (ref. 16), and it may be this dissipative process which is responsible for the retardation in sliding.

This result has implications for the study of stick-slip or intermittent sliding motion. This type of motion may occur when there are viscoelastic interactions between the machine and the sliding process^{17,18}. Simple analysis shows that it is present when a machine is subcritically damped and when either the static frictional force is greater than the dynamic or when the frictional force decreases with increasing sliding velocity. Because the frictional force is made up, in part, from a product of τ and the real area of contact, the retardation process may be an important factor in controlling its occurrence. In addition the experimental method seems to be useful for the study of the time-dependent properties of organic polymers.

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B. J. BRISCOE
A. C. SMITH

Department of Chemical Engineering
and Chemical Technology,
Imperial College, London SW7, UK

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IR studies of long-range surface effects—excess proton mobility in water in quartz pores

LONG-RANGE ordered elements of water structure of micro-metre dimensions have long been suspected to exist near certain aqueous/solid interfaces. However, the evidence has been inconclusive¹ and it has also been argued that such ordered elements of water structure exist near a glass surface from a comparison of the diffusion coefficients of the hydrogen ion from polarography and the sintered glass diaphragm cell method^{2–4,10}. The pore size of the sintered glass varied between 4 and 15 μm . The mobility of the hydrogen ion is known to be very sensitive to the structure of water^{5,6}. We present here convincing evidence from an IR spectroscopic study of 1M HCl in porous silica that such long-range ordering effects exist near a quartz surface and that as a consequence the excess proton mobility is reduced. Such long-range effects have not been conclusively demonstrated previously. With acid solutions the interaction between the easily polarisable hydrogen bonds of H_2O_2^+ groupings may favour such a long-range order and as the absorbance of the polarisable hydrogen bonds is sensitively influenced by all interaction effects this order may be indicated by changes of the IR continua.

The method of detecting long-range surface effects consists of measuring the absorbance of the continuous absorption observed in acid and base solutions beginning at 3,200 cm^{-1} and extending to smaller wave numbers. It has been shown⁷ that the

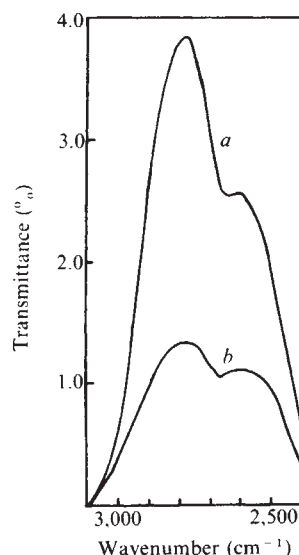


Fig. 1 Spectra of water (a) and 1M HCl (b), effective thickness $31.8 \pm 0.5 \mu\text{m}$, absorbed in porous quartz (pore size 4–15 μm).

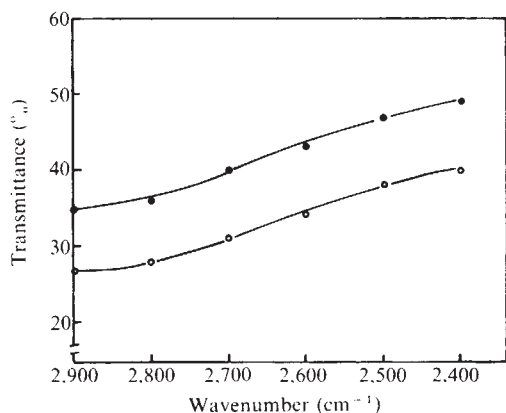
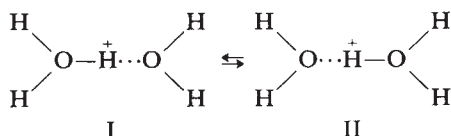


Fig. 2 Calculated difference spectra, that is the spectra of continuum for 1M HCl, effective thickness $31.8 \pm 0.5 \mu\text{m}$, absorbed in quartz pores (●); and for film of 1M HCl, thickness $32.0 \pm 0.2 \mu\text{m}$ between parallel silicon plates (○).

continuum is due to the H_5O_2^+ groupings in the case of acids and the H_3O_2^+ grouping in the case of bases. The phenomenon is not confined to acids and bases and has been observed whenever there is a grouping with a hydrogen bond in which a potential well with a double minimum or a flat broad potential well is present. Such cases have been observed in aqueous and non-aqueous solutions⁷. Furthermore, it has been demonstrated that such H-bonds are extremely easily polarisable. The polarisability of such H-bonds is about two orders of magnitude greater than the usual polarisabilities and hence they interact strongly with the environment, for example, by induced dipole interactions with ions and with dipole fields of the solvate and solvent molecules and particularly with each other. The energy surfaces of the easily polarisable hydrogen bond in H_5O_2^+ becomes strongly deformed by these interactions. As the strength of these interactions shows a broad distribution, a continuity of energy level differences occurs which is observed as continuum in the IR spectra. On the other hand, crystals containing H_5O_2^+ , for example, give broad bands⁸ in the IR spectrum instead of a continuous absorption because the H_5O_2^+ ions are held in rigid crystalline lattice and do not experience the fluctuating random electric fields of a solution. The presence of the continuum with aqueous acids indicates that protons are fluctuating between two boundary structures I and II



If the continuum decreases due to some external field this means that the hydrogen bond becomes polarised, the proton lingering time is greater at one of the two water molecules in the H_5O_2^+ grouping and the proton fluctuation frequency has decreased⁷. Consequently any influence which modifies the normal fluctuating structure of water containing, for example, H_5O_2^+ grouping should also influence the continuous IR absorption. If the influence structures the water causing an asymmetrical environment of the H_5O_2^+ groupings then the continuum should decrease and if, on the other hand, the influence renders the normal bulk structure of water containing the H_5O_2^+ groupings more random, then the continuum should increase⁹. Such effects have been observed on adding electrolytes to aqueous solutions of strong acids⁶.

Disks of sintered quartz 30 mm diameter and 4 mm thick (Heraeus) were each sliced into two disks of the same diameter as the original disk and the resulting disks were ground with a diamond wheel to a thickness between 130 and 100 μm . Only water without any additives was used in the cutting and grinding processes and the disks were held in a special holder without any

adhesive. After grinding, the disks were placed in water and treated with an ultrasonic vibrator to remove any loose particles. The ground disks were chosen for the IR study on the basis of the uniform appearance under the microscope. Water and 1M HCl were absorbed in the disks and the difference in weight between the wet disk, which was carefully blotted between filter papers, and the dry disk was determined. Using also the diameter of the disk, 30 mm, the effective thickness of the liquid could be calculated. For the IR measurements the porous quartz disk was held between thin clear optically flat quartz plates in a special holder to avoid evaporation.

The transmittance of the disks was $<4\%$ in the region $3,000\text{--}2,400 \text{ cm}^{-1}$ and hence it was not possible to obtain reliable spectra with an optical-null IR spectrophotometer. All spectra were obtained with an electrical-null, ratio-recording Perkin-Elmer 580 at an ordinate expansion of $20\times$. On the expanded scale the transmittance was reliable to 0.4% . The disk was placed in the sample beam and the transmittance recorded.

Figure 1 shows the spectra for water and 1M HCl absorbed in a porous quartz disk at an effective thickness of $31.8 \pm 0.5 \mu\text{m}$. Reproducibility was excellent. Figure 2 shows the calculated difference spectra (the spectra for the continuum) between 1M HCl and water absorbed in porous quartz ($31.8 \pm 0.5 \mu\text{m}$ thickness), and 1M HCl and water as thin films between silicon plates ($32.0 \pm 0.2 \mu\text{m}$ thickness). The two spectra are identical in shape but that for porous quartz shows a higher transmittance, that is the absorbance of the continuum for 1M HCl is less when

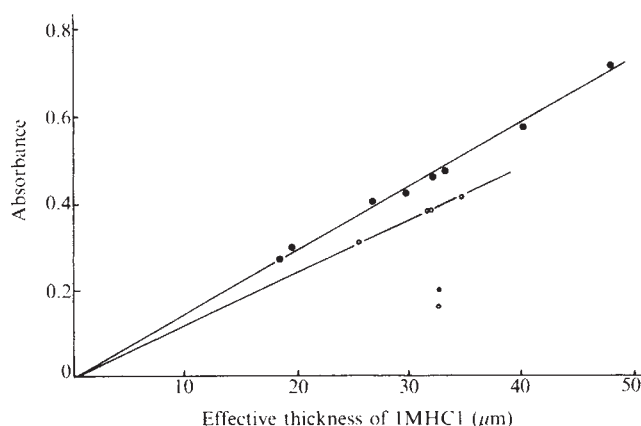


Fig. 3 Dependence of absorbance of continuum on effective thickness of 1M HCl at $2,560 \text{ cm}^{-1}$ absorbed in porous quartz (pore size $4\text{--}15 \mu\text{m}$) (○) and as film between silicon plates (●).

absorbed in porous quartz of $4\text{--}15 \mu\text{m}$ pore size range. The identical shapes of the spectra seem to eliminate optical effects as a cause of lower absorbance in porous quartz, as such effects are strongly wavelength dependent and would affect the shape of the spectrum differently at different wavelengths.

The absorbance of the thin films of 1M HCl and water between parallel silicon plates was determined with a special holder described previously⁶. Figure 3 shows the absorbance of the continuum of 1M HCl at $2,560 \text{ cm}^{-1}$ plotted against the effective layer thickness for 1M HCl as a film and absorbed in porous quartz. At all thicknesses studied, the absorbance of the continuum for 1M HCl absorbed in quartz was less than that for the film.

The large depression of the continuous absorption must be caused by a polarisation of the H_5O_2^+ groupings by their local environments. The fluctuation frequency of the excess proton between structures I and II is decreased. The only source of asymmetry of the local environments at the H_5O_2^+ groupings can be a long-range order of the liquid structure by the surface of the pores. Thus, the decrease in intensity of the continuum of H_5O_2^+ in quartz pores indicates the order which may be favoured by interactions of the easily polarisable hydrogen bonds with the environment and especially with each other.

In principle this method of observing long-range surface forces could be extended to non-aqueous systems containing a solute with a high polarisable H-bond. Zundel has discussed such systems elsewhere⁷.

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NOEL K. ROBERTS

Chemistry Department,
University of Tasmania,
Tasmania, Australia 7001

GEORG ZUNDEL

Physikalisch-Chemisches Institut der Universität München,
D-8000 München 2, Theresienstrasse 41, FRG

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Radiation-induced shrinkage of voids in molybdenum and TZM

SINCE the discovery of voids in neutron-irradiated stainless steels by Cawthorne and Fulton¹ considerable effort has been made to obtain experimental data on the nucleation and growth of voids and to understand the processes involved. The phenomenon has been of interest to the designers of fast reactors and could also be an important factor in material development for fusion reactor requirements. From both experiment and theory it is generally expected that for irradiations in constant temperature conditions, the voids will grow and the total void swelling increase with increasing displacement damage. Results are presented here which are contrary to this behaviour and show that in molybdenum and its alloy TZM (Mo, 0.5% Ti, 0.1% Zr), conditions exist where voids initially grow but then shrink as the irradiation proceeds.

High purity zone refined molybdenum² and TZM, both in recrystallised condition, were irradiated in the Dounreay fast reactor to total neutron doses of 1.5, 3.5 and $8 \times 10^{26} \text{ m}^{-2}$ giving calculated damage levels of 7.5, 17.5 and 40 displacements per atom respectively. The highest dose specimens were obtained by re-irradiating some of the specimens after the 3.5×10^{26} radiation. All the specimens discussed here were irradiated in

instrumented rigs at temperatures of $450 \pm 25^\circ \text{C}$. They were in the form of 3 mm disks and were examined after irradiation and after suitable electro-polishing by transmission electron microscopy in a Philips EM400 microscope. This system enabled voids with diameters $>0.8 \text{ nm}$ to be resolved.

The main results from the microscopy study are given in Table 1. The general result of a high density of voids and the appearance of loops agreed with previous high-dose neutron radiation studies of molybdenum and TZM near 450°C (refs 4–8). Similarly, the observation of void and loop lattices was not unusual. The unexpected result was the absence of visible voids in the high-dose TZM specimens. As it was known that these specimens contained voids before their second irradiation, it was at first thought that some aberration, such as a high temperature excursion (the most obvious way to remove voids) must have occurred. This was ruled out by two factors, namely the rig temperature records and the presence of voids in commercial molybdenum packing disks irradiated adjacent to the TZM specimens. However, when all the results are examined it becomes clear that the TZM result is the end product of a general irradiation process involving, first, the formation and growth of voids and, finally, their radiation-induced shrinkage. In the highest dose molybdenum specimen the large reduction in void swelling is clear but Table 1 also shows, when the void concentrations are examined, that the void shrinkage processes were already in operation during the medium dose irradiation. This is supported by evidence from void density histograms⁹ where the differences between the low and medium doses clearly show the simultaneous shrinkage of small voids and the continued growth of larger voids.

Some aspects of the dislocation loop structure are also of interest. The high loop density is evident in all the TZM specimens and also in the high-dose molybdenum shown in Table 1. The diameter of these loops, close to 5 nm, was surprisingly uniform. An important point was that the loops were indirectly established to be vacancy in nature; loop analysis procedures were carried out in annealed specimens where the fine loop structure had coarsened sufficiently to allow unambiguous identification. The loop lattice was apparent only in the presence of a void lattice. Since the results on molybdenum show the existence of a void lattice before loop growth, it implies that vacancy loop growth takes place preferentially on vacant void lattice sites.

The normal situation where voids acquire vacancies during the displacement damage process has been adequately explained elsewhere. The dislocations in the system have a preference, or bias, for interstitials leaving a supersaturation of vacancies to be captured by less biased, or neutral, sinks such as voids. To explain the observed void results, some mechanism must be invoked that allows a net flux of interstitials to the voids. It seems impossible to envisage any process taking place at a dislocation network to give this effect; instead such a situation is most likely to be achieved by some cumulative process inhibiting the jump of vacancies into a void. The presence of vacancy loops in the system supports this proposal. In particular it is significant

Table 1 The variation of void and loop parameters in Mo and TZM during neutron irradiation at 450°C

Material	Neutron dose (nm^{-2})	Average void size (nm) { $\pm 5\%$ }	Void density (m^{-3}) { $\pm 10\%$ }	Void swelling (%)	Loop density (m^{-3}) { $\pm 25\%$ }	Void/loop lattice parameter* (nm) { $\pm 5\%$ }
Mo	1.5×10^{26}	2.4	2.8×10^{23}	0.22	$\sim 6 \times 10^{20}$	22.2
Mo	3.5×10^{26}	4.4	1.3×10^{23}	0.57	$\sim 6 \times 10^{20}$	23.1
Mo	8.0×10^{26}	4.7	3.5×10^{22}	0.20	6×10^{22}	24.0
TZM	1.5×10^{26}	2.9	1.7×10^{23}	0.24	8×10^{22}	22.0
TZM	3.5×10^{26}	4.7	6×10^{22}	0.34	6×10^{22}	21.8
TZM	8.0×10^{26}	VNF	VNF	<0.01	1.3×10^{23}	—

VNF, voids not found.

* These values close to those suggested for 450°C by Moteff and Sikka³ who have studied the variation of void lattice parameter with irradiation temperature.

that the sharp rise in vacancy loop density in molybdenum takes place after void shrinkage processes have begun. If the voids acquire an effective preference for interstitials to add to the normal interstitial bias of the dislocation network, then it is not surprising that the vacancy concentration in the lattice could rise and allow the net absorption of vacancies in loops. However, the exact behaviour of the loops must clearly depend on their interstitial bias. It is interesting that the survival of the vacancy loops at a time when large voids are still growing (a situation certainly found in the medium-dose TZM specimens) supports the recent proposal¹⁰ that small vacancy loops must have a weaker interstitial bias than the network dislocations. The rather uniform loop size could also be significant in this context, as the vacancy loops might only grow to a size at which their neutrality with respect to the network is lost.

These results demonstrate that in both molybdenum and TZM, neutron irradiation can induce void growth and later, without any change in irradiation parameters, induce void shrinkage. A self-consistent explanation of the void and associated loop behaviour is that some mechanism first causes the smaller voids and later the larger to lower their probability of vacancy capture and hence allow a net influx of interstitials to their surfaces.

The void shrinkage in two materials of widely differing purity and the relatively slow increase in the effect during irradiation point to the mechanism being associated with the migration of transmutation products to the void surfaces. The segregation of alloying elements¹¹ and transmutation products¹² to voids by the flow of defects is already well known, but Marwick¹³ has recently derived expressions showing that solute atom segregation at voids can result in a void becoming biased against vacancies. Finally, if the effects reported here on molybdenum and TZM are found, or can be induced (perhaps by suitable alloy tailoring) in other materials, the technological interest could be considerable.

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J. H. EVANS

*Metallurgy Division,
AERE Harwell,
Oxon, UK*

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Table 1 Room temperature dissolution of candidate glass matrices

	High silica glass		Borosilicate glass	Others
	With barrier	Without barrier		
Matrix dissolution rate ($\text{g cm}^{-2} \text{d}^{-1}$)	5×10^{-10}	5×10^{-10}	10^{-5} to 2×10^{-7}	10^{-4} – 10^{-7}
Concentration of radioactive waste	0.5%*	15%	15–30%	15–30%
Rate of dissolution of waste material ($\text{g cm}^{-2} \text{d}^{-1}$)	2.5×10^{-12}	7.5×10^{-11}	3×10^{-6} to 3×10^{-8}	3×10^{-5} to 1.5×10^{-8}

* Concentration in the protective barrier; interior concentrations were at 15%.

emit all forms of radiation and therefore must be isolated from the environment. Most wastes are processed to salt form in aqueous, usually acidic solutions. The radioactivity levels of the waste materials in concentrated form are very high, with a high associated thermal power output¹. Waste forms may be kept at relatively cool temperatures (80 °C) with constant cooling. However, if cooling is not possible within the first century after removal from the reactor, the wastes may attain temperatures of several hundred degrees during this period. Although the actual thermal history of the solidified wastes is still a matter of debate it is becoming apparent that storage below 100 °C is desirable to maintain the structural and chemical integrity of the disposal medium. In addition, the fixation materials will receive high radiation doses and may undergo structural rearrangements. Finally, due to the constantly occurring radioactive decay processes, many isotopes will alter their chemical state and properties; most significantly, some species will give rise to secondary products in different physical states, such as the formation of He by α -emission. These transformations may stress the containers intolerably and lead to break-up or explosions which in turn expose a far larger surface area of the waste material to environmental attack. Therefore, the rate of chemical dissolution of the radioactive wastes in aqueous and saline solutions, and the structural stability, strength and He gas permeability of the various fixation materials determine the safety of the disposal systems for these wastes.

One promising approach to the problem of disposal is the process of fixation in oxide glasses². Glasses can withstand high ambient temperatures better than plastics or concrete, and have better durability than metals, especially in saline solutions. However, properties of glasses vary extensively with composition, and while glasses in general exhibit better chemical and physical durability than most other materials, a wide range of durabilities are possible depending on composition. For example, a glass such as B_2O_3 is immediately dissolved in water, yet other glasses show only small traces of corrosion even after millions of years³. In fact, with some glass compositions, the resistance to chemical attack achieved may be so high as to make possible beneficial uses of nuclear waste materials, such as for Cs and Sr radiation sources, without any danger of contamination of the environment.

The glass fixation schemes proposed in the past involve melting glass at relatively high temperatures⁴. Radioactive waste materials, however, must remain relatively cool to minimise the vapourisation of the volatile radioactive fission products including the alkali metals and the oxides of Ru. The most promising previous scheme using a zinc borosilicate glass was a compromise necessitated by the requirement to stay below 1,100 °C during melting². The compromise involved choosing a glass with very low silica content (<40%) to lower the melting temperature. The chemical durability exhibited by this glass, while better than that of many glasses, is considerably less than is achieved in good chemical labware, for example.

Good chemical durability in glass is generally achieved by

Fixation of radioactive waste in high silica glasses

THE safe disposal of large quantities of high-level radioactive wastes from spent power reactor fuels, or reprocessing is a problem of considerable concern because of the danger which may arise from their release into the environment. We describe here a multi-barrier vitrification process which is conducted at moderate temperatures (below 900 °C) and which yields the fixation of radioactive wastes as oxides in a high-silica matrix. Some special characteristics of this process are discussed, including the excellent chemical durability, high thermal and structural stability of the glass, and the possibility of multibarrier protection.

The waste materials contain a wide variety of isotopes which

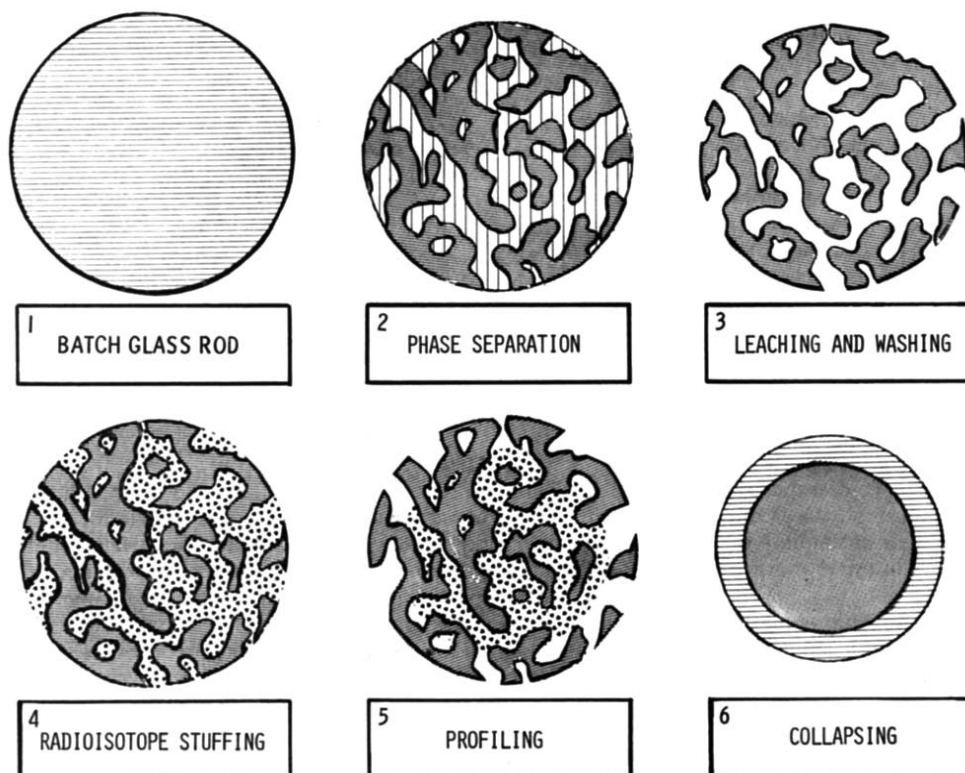


Fig. 1 Diagram of molecular stuffing process for the fixation of radioactive wastes.

increasing its silica content and decreasing alkali ion content as much as possible. This effect was observed with tektites retrieved from the ocean floor which show negligible chemical attack after 750,000 yr when the silica content is above 60% by weight⁵. These tektites, when measured in the laboratory, exhibit dissolution rates in water of approximately $0.5 \text{ \AA d}^{-1}$ (ref. 6).

Tektites have also provided information concerning the resistance of glass materials to devitrification over extended periods. Samples 35 Myr old have been found which are completely glassy and moon rocks have shown glassy phases over 4,000 Myr old without traces of crystallisation⁷.

The clue to high chemical durability and high structural stability seems to be high content of silica and other glassformers and low content of the alkali metals and other structure modifiers. Preliminary measurements of the compaction of glasses under high-level irradiation have shown that silica glass undergoes relatively little change⁸. Therefore, it is clear that high silica glasses will optimise the properties which characterise a desirable material for the fixation of radioactive wastes. However, preparation has been a problem since high temperatures (1,800 °C) are needed to melt glasses with a high silica content.

Recent research with a process for adding dopants to high silica porous glasses at relatively low temperatures (below 900 °C)⁹ has led us to develop a method suitable for the fixation of radioactive waste materials in a high silica glass.

The process uses a high-silica porous glass which can be prepared by melting an alkali-borosilicate glass, heat-treating it to induce phase separation into a high silica and a low silica phase and dissolving the latter by leaching in an acid solution which does not attack the high-silica phase. A porous glass with an interconnected porous structure and pore sizes from 100 to 500 Å is thus formed and consists of 96% SiO_2 and 4% B_2O_3 . (The melting, phase separation and leaching operations are shown in steps 1, 2 and 3 of Fig. 1.) These steps are non-radioactive and may be conducted in a separate plant. Step 1 which requires a temperature of 1,400 °C, however, causes no problem of volatilisation of toxic materials since this is a simple non-radioactive glass melting operation.

The porous glass is then taken to a waste fixation plant and is subsequently soaked in a solution containing the prescribed

radioactive waste materials in salt form (see Fig. 1, step 4). These can be nitrates or other salts which decompose to oxides below 700 °C. After a soaking period of several hours, which allows the pores to fill completely with the solution, the laden porous glass is removed from the solution and the salts present in the pores are precipitated by undercooling. The porous glass is then soaked in a clean solvent which removes the waste material salts from an outer layer of porous glass at the surface of the glass object (see Fig. 1, step 5). The solvents are subsequently evaporated and the porous glass is heated slowly to between 625 and 700 °C to complete the drying and to decompose the waste material salts to an oxide form. Further heating to 900 °C sinters the structure by viscous flow, thus collapsing the pores and yields, on cooling, a solid glass object containing the radioactive waste materials interstitially in the interior (core region) and a high silica envelope on the outer surface (cladding region) (see Fig. 1, step 6). The core region consists of 75% SiO_2 and approximately 20% radioactive waste loading; the cladding region consists of 95% SiO_2 and is relatively free of waste materials (less than 0.5%). The cladding region can be made with any desired depth. An additional benefit of the difference in composition between the core and the cladding regions is the large surface strengthening obtained in these samples arising from a difference in the contraction of the two regions in cooling after fabrication. The clad region being of higher silica content has a lower coefficient of thermal expansion and is therefore fabricated with a large surface compressive stress which enhances the strength and stress corrosion resistance of these samples¹⁰.

We have made many samples with a number of dopants, most notably caesium oxide because it poses a significant problem as a radioactive waste material with its low vaporisation temperature, its high diffusion coefficient in glass and its high level of γ -radiation.

When caesium was used as a single dopant, the caesium oxide distribution in the finished rods was 15% by weight in the core and <0.5% in the clad, with the remainder of the glass being 4% B_2O_3 and the rest silica. (Note that this is a concentration of SiO_2 above 90 mol per cent.) We report, below, data on caesium-doped samples. We have also made samples containing mixtures of Fe, Sr, Y, Zr, Cs, Ba, La, Ce and Nd as nitrates, simulating a

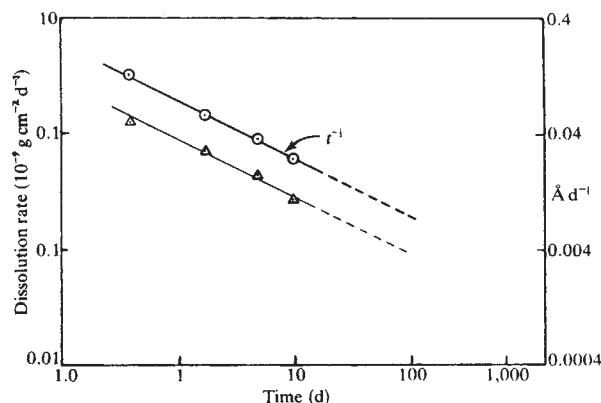


Fig. 2 Time dependence of room temperature dissolution rates for a high-silica glass matrix and for one with a 15% dopant concentration. O, Doped glass (15% loading); Δ, base glass.

Pw7-a waste stream² with equally successful results.

We have tested the chemical durability of rods containing 15% Cs₂O and rods without dopant by immersing them in distilled water at room temperature and at 100 °C for various times up to 10 d in a Teflon beaker. The chemical durability was related to the amount of silica released by the rods into the distilled water. The dissolution rate at room temperature is shown in Fig. 2 as a function of time for both types of glass. After 10 d in water, at room temperature the dissolution rate of the loaded rod is down to 0.02 Å d⁻¹ (5×10^{-10} g cm⁻² d⁻¹) following a square root behaviour with time. The base glass dissolution rate is down to 0.01 Å d⁻¹ after the same time period. At 100 °C the dissolution rate of the doped glass was measured to be 4×10^{-6} g cm⁻² d⁻¹ after 2 d and 2×10^{-6} g cm⁻² d⁻¹ after 4 d.

There are two mechanisms which may control the rate of release of caesium into the bath. The first corresponds to caesium ion diffusion through the glass to the surface, while the second corresponds to the dissolution of the surface itself. The diffusion coefficient for caesium in this glass at 20 °C has been estimated to be 1×10^{-29} cm² s⁻¹ from electrical conductivity measurements¹¹. This predicts a caesium release rate of 3×10^{-18} g cm⁻² d⁻¹. This value is so small that despite the wide discrepancy usually seen between diffusion coefficients calculated from conductivity measurements and leach rate measurements, it is most likely that the rate of release of caesium from the cladding region of the glass into the bath will be controlled by the rate of surface dissolution and will have a value of 2×10^{-12} g cm⁻² d⁻¹ at room temperature. This number is the product of the measured dissolution rate (5×10^{-10} g cm⁻² d⁻¹) and the caesium concentration in the clad (0.5%). Since the cladding region is expected to be 1 mm thick, it will take over 1 Myr to dissolve it.

The matrix dissolution rates measured for these samples are extremely low—lower than those measured for long-lived geological glass specimens. Compared to the other glass media being considered for radioactive waste fixation (see Table 1), these high silica glasses exhibit matrix dissolution rates 1,000-fold lower, in comparable conditions, without the additional benefit of the protection which the cladding region offers. As the cladding region developed by this process only contains 0.5% loading, then until the entire clad has been leached, the dissolved glass only contains a 0.5% concentration of waste materials while the glasses without the protective barrier contain concentrations of 15–30%. This provides an additional reduction by a factor of 30–60 in calculating the rate of release of waste materials from glasses made by the molecular stuffing process, giving a cumulative improvement of 10,000 to 1,000,000 times other glass encapsulation processes (see Table 1). Note that even without the barrier, improvements between 300 and 30,000 are still obtained.

These results show that the high-silica glass matrix produced

by the porous glass process could be of value for effective long-term chemical fixation of radioactive wastes. Several questions remain to be studied, such as the effect on durability of pressure, of high levels of radiation and of chemical transmutations.

In conclusion, we have demonstrated that the fixation of radioactive wastes is feasible in high-silica glasses of good chemical durability. An analysis of leaching rates measured on this high-silica glass shows a clear advantage over other fixation media.

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JOSEPH H. SIMMONS
PEDRO B. MACEDO
AARON BARKATT
THEODORE A. LITOVITZ

Vitreous State Laboratory,
Catholic University of America,
Washington, DC 20064

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Is CS₂ a precursor for atmospheric COS?

THE stratospheric sulphate layer¹ may play a major part in the Earth's global radiation budget^{2,3}. Recent measurements^{4–6} indicated that carbonyl sulphide (COS) has an appreciable concentration, ranging from 0.3 to 0.5 p.p.b. in the Earth's troposphere. The gas is relatively inert^{7,8} in the troposphere and may therefore diffuse to the stratosphere where, through photolysis^{7–9}, it may provide a major source of sulphate for the formation of the stratospheric sulphate layer. Thus, the origin of atmospheric COS is of particular interest in the stratospheric sulphur cycle. Kurylo¹⁰ suggested that the reaction of carbon disulphide (CS₂) with OH might form COS as a reaction product. We investigate this possibility here through global COS budget analysis in the light of new atmospheric and laboratory measurements. Recent measurements showed that CS₂ has a tropospheric concentration of around 0.1 p.p.b.⁵. The gas has previously been detected in seawater samples by Lovelock¹¹. These measurements seem to suggest that the ocean might be a source for atmospheric CS₂.

The atmospheric sinks for COS are,



and



Reaction (1) dominates in the stratosphere and may account for a global removal rate of COS of about 2.4×10^4 ton (S) yr⁻¹ based on our 1-dimensional model calculation¹² using measured photolysis cross-sections^{13,14}. Reaction (2) is relatively unimportant. The rate constant k_3 for reaction (3) is uncertain. Removal of COS in the troposphere, however, could be dominated⁸ by reaction (3) if k_3 exceeds 1×10^{-15} cm³ s⁻¹. Kurylo¹⁰ recently reported a value of 5.7×10^{-14} cm³ s⁻¹ for

k_3 at 296 K, in apparent conflict with an upper limit $k_3 \leq 7 \times 10^{-15} \text{ cm}^3 \text{ s}^{-1}$ reported by Atkinson *et al.*¹⁵. Assuming a tropospheric OH abundance¹⁶⁻¹⁸ of 10^6 cm^{-3} , one would estimate global removal rates of COS due to reactions (1-3) of $\sim 2.2 \times 10^6 \text{ ton (S) yr}^{-1}$, $2.2 \times 10^5 \text{ ton (S) yr}^{-1}$ and $2.4 \times 10^4 \text{ ton (S) yr}^{-1}$ corresponding to the cases $k_3 = 5.7 \times 10^{-14} \text{ cm}^3 \text{ s}^{-1}$, $k_3 = 5 \times 10^{-15} \text{ cm}^3 \text{ s}^{-1}$ and $k_3 = 0 \text{ cm}^3 \text{ s}^{-1}$ respectively. The obvious question is whether one can account for the global COS balance in each of the above three cases representing different atmospheric lifetimes of COS.

Atmospheric oxidation of certain sulphur-carbon containing species such as CS_2 and DMS (CH_3SCH_3) might be possible sources for atmospheric COS. For instance, the reaction of CS_2 with OH,



might produce COS^{10} . The rate constant k_4 is $1.85 \times 10^{-13} \text{ cm}^3 \text{ s}^{-1}$ according to Kurylo¹⁰ and $\leq 7 \times 10^{-14} \text{ cm}^3 \text{ s}^{-1}$ according to Atkinson *et al.*¹⁵. The products in reaction (4) have not been identified. However, note that reaction (4a) is endothermic¹⁰ by 23 kcal mol^{-1} , while (4b) is exothermic¹⁰ by 35 kcal mol^{-1} . Assuming that reaction (4) proceeds primarily through branch (4b), the flux of COS obtained from integrating the continuity equation is

$$\phi_{\text{COS}}(z=0) = \int_0^\infty \{k_3[\text{OH}][\text{COS}] + J[\text{COS}] - k_{4b}[\text{OH}][\text{CS}_2]\} dz \quad (5)$$

Where J is the photolysis rate of COS and $[i]$ denotes the concentration (molecule cm^{-3}) of the species i . The quantity ϕ_{COS} defined here may be interpreted as a measure of the deficit in the COS budget and may be readily calculated using a standard one-dimensional model¹². If we adopt the observed mixing ratios of COS and CS_2 of 0.4 and 0.1 p.p.b. (parts per 10^9) (refs 4-6) respectively, a first order balance in COS budget may be achieved by adjusting the values k_3 and k_{4b} . For instance, in the above three cases where $k_3 = 5.7 \times 10^{-14} \text{ cm}^3 \text{ s}^{-1}$, $5 \times 10^{-15} \text{ cm}^3 \text{ s}^{-1}$ and $0 \text{ cm}^3 \text{ s}^{-1}$, the corresponding values for k_{4b} have to be 1.7×10^{-13} , 1.7×10^{-14} and $2 \times 10^{-15} \text{ cm}^3 \text{ s}^{-1}$ to balance the COS budget. Note that for the first case, the pair of values (k_3 , k_{4b}) is consistent with the values reported by Kurylo¹⁰. While the values for the two latter cases are consistent with the upper limits set by Atkinson *et al.*¹⁵.

Note that when reaction (3) is the dominant loss process for COS ($k_3 \geq 2 \times 10^{-15} \text{ cm}^3 \text{ s}^{-1}$), a simple relationship between the ratios k_3/k_{4b} and $[\text{CS}_2]_0/[\text{COS}]_0$, where the subscript '0' denotes surface concentration, can be derived from the consideration of COS budget balance. When $\phi_{\text{COS}} \approx 0$ (that is: approximate balance), equation (5) becomes

$$\int_0^\infty k_3[\text{OH}][\text{COS}] dz \approx \int_0^\infty k_{4b}[\text{OH}][\text{CS}_2] dz \quad (6)$$

from which we can derive a ratio $[\text{CS}_2]_0/[\text{COS}]_0$ which is independent of OH concentration by noting,

$$k_3[\text{OH}]_0[\text{COS}]_0 H_3 \approx k_{4b}[\text{OH}]_0[\text{CS}_2]_0 H_{4b} \quad (7)$$

where H_3 and H_{4b} are the appropriate scale heights for reactions (3) and (4b) respectively. Since H_3 and H_{4b} are of similar order, the ratio $[\text{CS}_2]_0/[\text{COS}]_0$ is given by

$$R_A \equiv \frac{[\text{CS}_2]_0}{[\text{COS}]_0} \approx \frac{k_3}{k_{4b}} \equiv R_L \quad (8)$$

Equation (8) relates an atmospheric quantity R_A with a laboratory quantity R_L and confirmation of equation (8) will strongly suggest CS_2 as a precursor for COS. Clearly, measurement of k_{4b} requires the detection of COS as a product from reaction (4).

The only atmospheric CS_2 data reported to date are those by Sandalls and Penkett⁵, which seemed to be quite scattered with values ranging from 0.07 to 0.2 p.p.b. However, the lower values should be more appropriate for global conditions. Taking a typical COS concentration⁴⁻⁶ of ~ 0.4 p.p.b. the ratio R_A is $\sim 0.18-0.5$ in harmony with the quantity, $R_L = 0.3$ derived from laboratory measurements of k_3 and k_{4b} by Kurylo¹⁰. In view of the present uncertainties in both atmospheric and laboratory data, the agreement between R_A and R_L may be fortuitous. Nevertheless, relation (8) and similar analysis on other sulphur-carbon containing species (for example, DMS) would provide useful guidelines for identifying the appropriate atmospheric and laboratory measurements which may lead to a better understanding of the origin of COS, and might have interesting implications on the origin of the stratospheric sulphate layer.

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NIEN DAK SZE
MALCOLM K. W. KO

Atmospheric and Environmental Research, Inc.,
872 Massachusetts Avenue,
Cambridge, Massachusetts 02139

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⁸⁷Rb-⁸⁷Sr age of Saint Mesmin chondrite and dating of gas-rich polymict breccia

CHONDRITES are generally regarded as being the oldest objects in the Solar System. However, most of them have suffered severe secondary effects, such as metamorphism, shock and irradiation. The gas-rich polymict breccias have had the most complex history of the chondrites. Some grains of polymict breccias have been exposed to solar irradiation and trapped solar-type rare gases before compaction of the meteorite. Evidence indicates that they were formed in a regolithic environment at the surface of their parent body¹. However, the timing of the successive events which affected the gas-rich chondrites is largely unknown. Saint Mesmin (chemical group LL), is probably the best studied example²⁻⁷ of this class of meteorites. It consists of a dark matrix, rich in solar-type noble gases, which contains light gas-poor xenoliths². The matrix is mineralogically unequilibrated and its material belongs to the chondritic petrological types 4 and 5 (ref. 3). In contrast the xenoliths have been strongly metamorphosed and re-equilibrated and belong to the petrological types 6 and 7 (ref. 3). Also veins of olivine microporphyry run across the meteorite³. Finally, a tectonically incorporated piece of chondrite, of the chemical group H (type H4), has been found in Saint Mesmin⁴. Here, we deal with ⁸⁷Rb-⁸⁷Sr dating of small 10 mg, hand-picked pieces, of the various components of Saint Mesmin. These pieces have been

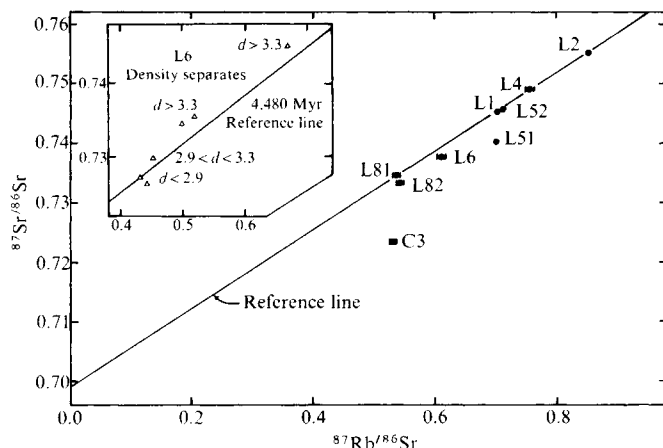


Fig. 1 $^{87}\text{Sr}/^{86}\text{Sr}$ versus $^{87}\text{Rb}/^{86}\text{Sr}$ plotted for the light xenoliths. Sample names are as given in other studies³⁻⁷. Two digit numbers indicate independent analyses for the same xenolith. Petrographic type is 7 for C3 and L2, 6 for the others³. The inset shows the data for the heavy liquid separates from the L6 xenolith. Reference line: 4,480 Myr; $\lambda = 1.42 \times 10^{-11} \text{ yr}^{-1}$; $^{87}\text{Sr}/^{86}\text{Sr} = 0.69877$.

studied by the other techniques³⁻⁷ and have been named by Pellas. Light xenoliths are labelled L1 to L8 and dark samples D1 to D8. One particular light xenolith of petrological type 7 is named C3. Two samples of the type H4 xenolith are named D1 and DD respectively. Where several pieces of the same sample had been analysed independently, we added a second digit to the sample name (for example L81 and L82). We have also analysed heavy liquid fractions of one light xenolith (L6) and of one sample of the H4 type xenolith (DD).

Experimental techniques follow those of Birck and Allègre⁸ and those reported elsewhere⁹. In this study, however, dissolution has only been made in a HF-HNO₃ mixture. New columns and labware meant that some blanks were high (up to 0.1 ng Rb and 0.4 ng Sr) compared with our usual ones (0.05 ng Rb and 0.1 ng Sr).

The results are given in Figs 1 and 2 for light xenoliths and dark samples respectively. (Raw data may be obtained from the authors.) Data for the light xenoliths scatter in the $^{87}\text{Rb}/^{86}\text{Sr}$, $^{87}\text{Sr}/^{86}\text{Sr}$ diagram (Fig. 1). However, most of them plot on a line of age 4,480 Myr ($\lambda^{87}\text{Rb} = 1.42 \times 10^{-11} \text{ yr}^{-1}$), not significantly different from our 'primitive isochron' for chondrites⁹. Our data for heavy liquid density fractions, from the L6 xenolith, are shown on both sides of the reference isochron (inset). If we assume that experimental perturbations by heavy liquids have been negligible, this scatter shows that the ^{87}Rb - ^{87}Sr clock has been partially reset. The repartition of the points can indicate that Rb and Sr redistribution has been closed at the scale of the xenolith. As our samples are rather small, they are probably unrepresentative of each light xenolith. As most of the data plot on the 4,480 Myr reference line this can indicate that all xenoliths are that old, but that the ^{87}Rb - ^{87}Sr system has been perturbed between the minerals of some or all of them. This is also supported by the 4,500 Myr old ^{87}Rb - ^{87}Sr age of Saint Mesmin whole rock¹⁰.

Similarly, samples of the dark components do not define a straight line in Fig. 2. These dark components are, however, of various types: D7 and D8 are samples of the gas-rich matrix; whereas D7 plots on the reference line at 4,480 Myr (samples D71 and D72), D8 plots significantly below (samples D81 and D82). This reveals that the ^{87}Rb - ^{87}Sr system in the matrix has been perturbed at a time younger than 4,480 Myr.

D6 is a gas-poor black xenolith⁷. Our two analyses (D61 and D62) plot on both sides of the reference isochron. As for black hypersthene chondrites¹¹, this result could indicate when this black xenolith was reheated. The slope of the two point-line defined by D61 and D62 yields an age of 1,500 Myr.

Samples of the two microporphyric inclusions D3 and D5 have been analysed⁶. All of them (D3, D51 and D52) plot on the reference isochron. This agrees with their old K-Ar as well as their ^{39}Ar - ^{40}Ar ages^{7,12}. This result is of great importance as these inclusions have been melted and have intruded the meteorite after some brecciation has already occurred⁶. It seems therefore, that the meteorite was brecciated very early in its history. It is interesting that the dark parts of Krähenberg, which are similar to these microporphyric inclusions⁶, also have a 4,600 Myr-old ^{87}Rb - ^{87}Sr age¹³, although this measurement lacks accuracy. Assuming that LL chondrites have had a single parent body, this could indicate that a melting event occurred quite early in its history, and that the melt intruded these two meteorites.

Finally, we have analysed the H4 xenolith (samples D1 and DD), as well as heavy liquid density fractions from sample DD (inset). Whereas the analyses for the whole rock and the heavy fractions of the comparatively large (70 mg weight) sample DD plot on the reference isochron, that for the smaller sample D1 plot well below this line. Figure 3 shows that Rb and Sr are mainly contained in two mineral phases of the xenolith. Whereas the heavier fraction (olivine?) forms an Rb and Sr - poor abundant reservoir, fraction $2.9 < d < 3.1$, consists of Rb- and Sr-rich sparse minerals. The abundances of Rb and Sr in sample D12 (Fig. 3), as well as the position of this sample in the ($^{87}\text{Rb}/^{86}\text{Sr}$ against $^{87}\text{Sr}/^{86}\text{Sr}$) diagram (Fig. 2, inset), indicate that the second phase is enriched in D12 compared with sample DD. Thus, D12 is probably unrepresentative of the average xenolith. Our data on sample DD indicates that this H4 xenolith of Saint Mesmin is about 4,500 Myr old. Its ^{87}Rb - ^{87}Sr system has been perturbed later, possibly due to post-shock reheating. Note that the age defined by DD and the Rb and Sr-rich fraction ' $2.9 < d < 3.1$ ', is 1,200 Myr which roughly agrees with the 1,400 Myr K-Ar age of this xenolith. The strong orientation of the metallic patches in DD indicates that it has been severely shocked. As there is no clear effect in the adjacent parts of the meteorite, DD was probably shocked before its incorporation in Saint Mesmin, and possibly inside the H-chondrite parent-body, 1,400 Myr ago.

Dodd and Jarosevitch⁶ suggest that at least two brecciation events affected the microporphyric inclusions of Saint Mesmin. As discussed above, a first brecciation occurred very early in the history of this meteorite. Our data are ambiguous with regard to younger episodes. First we consider the model ages of our samples relative to the $^{87}\text{Sr}/^{86}\text{Sr}$ initial ratio of chondrites, $^{87}\text{Sr}/^{86}\text{Sr} = 0.69877$ (refs 9, 14). Except for sample C3, they are all older than 4,000 Myr. This could indicate that the irradiation and brecciation history of Saint Mesmin is that old. Such a model

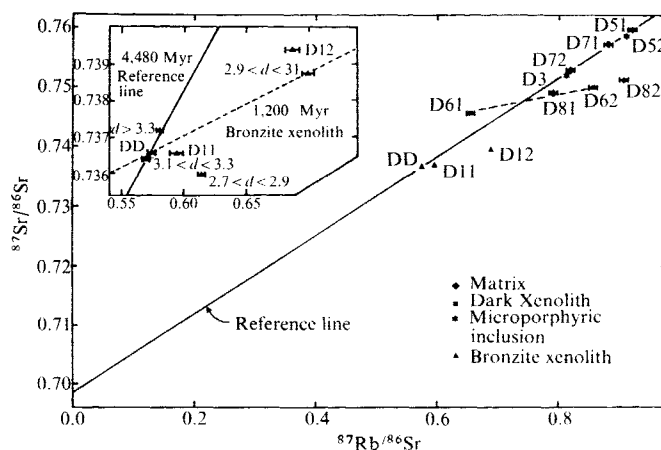


Fig. 2 $^{87}\text{Sr}/^{86}\text{Sr}$ versus $^{87}\text{Rb}/^{86}\text{Sr}$ plotted for the dark xenoliths. For general information see Fig. 1. The inset shows the data for the H-type xenolith.

has been supported by Pellas from U-Th-He and K-Ar data older than 4,000 Myr for most of these samples⁴. However, the two-point isochron of the D6 xenolith may be significant. With the data of the H4 xenolith (sample DD) this can indicate that Saint Mesmin was not yet compacted at that time, and was situated close to the surface of its parent body. This has been argued by Schultz and Signer⁷ on the basis of the K-Ar Age of the H4 xenolith.

Saint Mesmin is composed of 4,480-Myr-old components, many of which have been subsequently thermally disturbed. The foreign H type component can be understood as a residue of an impacting body at the surface of the Saint-Mesmin parent-body. Although their interpretation is not unique, the chronological

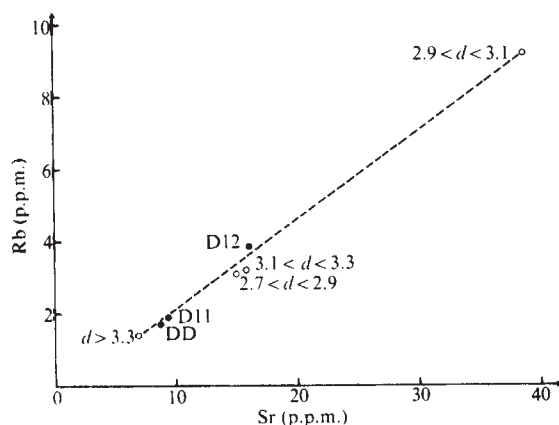


Fig. 3 Sr/Rb diagram for the samples and the density separates from the H4 type xenolith. Any fraction can be considered as a mixture of two main minerals respectively contained in fractions $d > 3.3$ and $2.9 < d < 3.1$. D12 is an unrepresentative sample of the mean xenolith.

data support a formation of Saint Mesmin from a regolith at the surface of its parent planet, as recently as 1,400 Myr ago. In particular, the chronological data indicate that the solar irradiation of some grains from the matrix does not correspond to an early irradiation, such as a T-Tauri phase of the Sun.

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J. F. MINSTER

C. J. ALLEGRE

*Laboratoire de Géochimie et Cosmochimie,
Institut de Physique de Globe et
Département des Sciences de la Terre,
Universités Paris VI et VII,
4 Place Jussieu, 75005 Paris Cedex 05, France*

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A Morarian age for the 'younger Moines' of central and western Scotland

MUCH of our recent knowledge of the Moine metasediments^{1,2}, which extend from the Moine Thrust across the Great Glen Fault to the boundary of the Dalradian Supergroup^{3,4} (Fig. 1), stems from the western Moine region. Here, late-Precambrian, Morarian ages (740-780 Myr) have been established from pegmatites in the Morar Division⁵, and a Grenvillian age ($1,030 \pm 50$ Myr) from the Granitic Gneiss of Ardour in the Glenfinnan Division⁶. The 'Central Highland Granulites', generally regarded as 'younger Moine'^{2,6}, are little known geologically. Here we briefly outline the results of field (by M.A.J.P.) and radiometric investigations (by O.v.B.) in the Central Highland Granulites and the western Moines, which have fundamental implications for the evolution of these extensive metamorphic rocks, and for the nature of the Grenvillian-Caledonian interval in this sector of the North Atlantic Crust.

Field relationships in the Central Highlands Granulites indicate that the region consists of two fundamentally different assemblages of Moine rocks: a basement, and an overlying cover (Fig. 1). The new name 'Central Highland Division' is used here to describe the basement rocks following Johnstone's use of the term division^{1,7}. The basement and cover are separated everywhere by a zone of tectonic break, called the Grampian Slide. Harris *et al.*⁴ have proposed using the lithostratigraphical term 'Grampian group' for rocks which clearly correspond with the cover assemblage, and their incorporation into the Dalradian

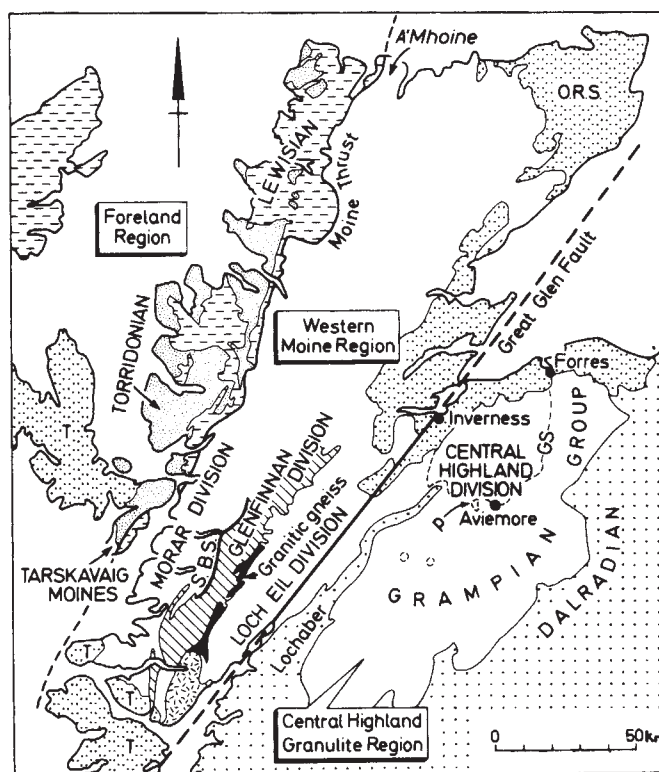


Fig. 1 Sketch map showing the geological setting of the Central Highland Division and the Grampian group: the Central Highland Granulite Region encompasses the outcrop areas of both. P, by Aviemore, centre of the Spey-Dulnain region; GS, approximate trace of the Grampian Slide; ORS, Old Red Sandstone; T, Tertiary and Mesozoic.

Table 1 Rb–Sr isotopic data for muscovite samples in pegmatites

Pegmatite no. and locality	Geological setting	Muscovite sample no.	Rb (p.p.m.)	Sr (total) (p.p.m.)	$^{87}\text{Rb}/^{86}\text{Sr}$	$^{87}\text{Sr}/^{86}\text{Sr}$ (Ri = 0.710)	Apparent age (Myr $\pm$ 0.007)
AB 4 (NH 79500920)	Basement	A	364	13.9	80.64	1.3683	573 $\pm$ 13
		B	367	20.0	62.18	1.2365	594 $\pm$ 13
		C	376	17.0	67.84	1.3303	640 $\pm$ 13
AB 90 (NH 79070937)	Basement	A	320	15.6	62.65	1.3071	668 $\pm$ 13
		B	329	14.1	72.30	1.4201	688 $\pm$ 13
DR 11 (NH 77291305)	Host uncertain	A	450	12.6	113.64	1.7005	611 $\pm$ 11
AF 20 (NH 77821126)	Cover–basement contact	A	317	17.7	54.35	1.1983	630 $\pm$ 14
		B	358	12.9	86.92	1.5695	693 $\pm$ 12
AF 20/8 (NH 77821126)	Cover	A	308	30.6	29.99	1.0116	705 $\pm$ 19
		B	305	29.2	31.13	1.0290	718 $\pm$ 19

All ages calculated with $\lambda^{87}\text{Rb}$ of $1.42 \times 10^{-11} \text{ yr}^{-1}$. Pegmatites AF20, AF20/8 have well preserved *D2* fabrics; in AB4, AB90, *D3* fabrics modify *D2*. DR11 is crenulated and retrogressed by a later, post *D3* event.

Supergroup. We prefer to describe the cover rocks informally, as the 'Grampian group'.

The Central Highland Division forms most of the ground between Inverness, Forbes and Aviemore (Fig. 1). Its dominant rocks are coarse to medium grained, variably gneissose siliceous and quartzofeldspathic metasediments which usually contain variably deformed concordant migmatite. These are interfolded with coarse, commonly migmatitic, quartzites, and with belts of coarse pelitic biotite-gneisses which frequently bear tabular kyanite and sillimanite.

In contrast with the basement, the rocks of the extensive Grampian group are finer grained, less metamorphosed, structurally simpler and essentially non-migmatitic. They form major formations of siliceous flags, semipelitic flags and pelitic schists. The presence of sedimentary structures in most lithologies should make it possible to elucidate regional tectonics and lithostratigraphical successions in this extensive region⁷. Mapping shows that some of the thick pelitic belts of the Central Highland Granulites generally thought to be Dalradian infolds in the Moines^{2,3,8}, such as the 'Grantown Series' and the Ord Ban-river Dulnain belt⁹, belong to a low stratigraphical level in the Grampian group and young upwards without a break into some of the Eilde Flags^{2,7,8}. Reconnaissance indicates that other pelitic belts, such as the Slochd–Streens of Findhorn^{7,9}, belong to the Central Highland Division.

Key evidence for the age relationships of these two rock assemblages stems from structural–metamorphic, stratigraphical and radiometric studies in the Spey–Dulnain watershed (centred on P in Fig. 1), where a late upfold brings up a core of Central Highland Division rocks within the Grampian group in the form of a tectonic window⁷. In this window, at least three very early generations of structures can be recognised, each associated with high-grade metamorphism. The earliest of these is a regional gneissosity. The second takes the form of penetrative isoclinal folding of this gneissosity, associated with migmatization and a high degree of mobilisation. The third forms a large regional recumbent fold which refolds the earlier structures.

The rocks of the Grampian group do not share these structures: they young consistently upwards for more than 1.5 km above their tectonic base, and lack intensive folding. Their earliest folds are associated with cover–basement sliding which truncates, shears out and superimposes new foliations on the early structures in the underlying basement. This contrast in the structural and metamorphic complexity between the Central Highland Division and the Grampian group is best interpreted in terms of an older basement separated by sliding from a younger cover.

In this Grampian group, the schistosity (*S1*) of the earliest deformation, *D1*, is highly overprinted by the effects of a major

event, *D2*. *S1* can only be seen where it is folded around the hinges of *F2* folds, and no *F1* folds have been found. *D2* resulted in a regional schistosity subparallel to the bedding, accompanied by kyanite-grade amphibolite facies metamorphism and by sliding in the cover–basement contact zone, where *D2* fabrics are those of coarse, platy-tectonic schists.

A subsequent major event, *D3*, resulted in a new regional schistosity associated with lower grade amphibolite facies metamorphism and renewed sliding in the Grampian Slide zone. *D3* sliding was associated with the growth of a penetrative fabric of replacement muscovite in the movement zones. In the tectonic schists, the *D3* overprint of *D2* produced platy muscovitic *D3* fabrics, in which *D2* fabrics are granulated and aluminosilicates are retrogressed. Subsequent deformations will be described elsewhere.

In this region, the *D2*–*D3* Grampian Slide forms a zone 30–200 m thick, in which both basement and cover rocks are variably tectonised into tectonic schists, and in which tectonic slices of basement are present in the cover rocks.

In this slide zone a distinctive suite of concordant–subconcordant foliated pegmatite veins occurs at localities as far as 60 km distant⁷. The pegmatite veins, 1 cm to 7 m thick, are present in both tectonised basement and cover rocks. They do not appear above or below the slide zone, and are interpreted as a syntectonic suite emplaced into movement zones. Rb–Sr analyses of 10 muscovite samples from five foliated pegmatites in the Dulnain watershed (Fig. 1) yield a grouping of ages within the range 718 $\pm$ 19 Myr to 573 $\pm$ 13 Myr (Table 1). The spectrum of ages in individual pegmatites corresponds with field distribution of *D2* and *D3* strains in the rocks of the slide zone. The higher ages are from pegmatites which share well preserved *D2* slide-fabrics with surrounding tectonised rocks. Conversely, the lower ages come from pegmatites in zones more thoroughly modified by the later *D3* fabrics.

This limited spread of ages indicates that the age of pegmatite emplacement into the movement zone, and the age of the *D2* sliding, are unlikely to be much older than 718 $\pm$ 19 Myr. Thus, the pegmatites and the *D2* event correspond with the Morarian ages of pegmatites in the western Moine region⁵. The same age pattern also implies that the *D3* event which partly resets the radiometric clocks in retrogressive metamorphic conditions accompanied by liberal fluid activity, is younger than 573 $\pm$ 13 Myr, and is therefore clearly Caledonian.

It follows that the cover rocks of this region—rocks belonging to the lower part of the Grampian group—are older than the Morarian pegmatites. Correspondingly, as already indicated, the Grampian group cover is believed to be younger than the Central Highland Division basement. We tentatively correlate the latter with the strikingly similar Glenfinnan Division rocks from which the Grenvillian (1,030 $\pm$ 50 Myr) migmatitic

Granitic Gneiss of Ardour (Fig. 1) is thought to have developed *in situ*^{6,7,14}.

Viewed in this light, the D1–D2 events in the Grampian group fall within the Grenvillian–Caledonian interval, and are considered here to signify the reality of a limited orogenic event of Morarian age (broadly between 750 and 850 Myr) within the Moines (see ref. 5). Additional support for such a Morarian event comes from recent Rb–Sr whole-rock analyses of large samples of semipelites from the north-east Ox Mountains and Lough Derg inliers in western Ireland. These data yield an 860 ± 115 Myr isochron and indicate a post-Grenvillian maximum age (M. B. Max and C. D. Long, personal communication).

Field and radiometric evidence therefore indicate that at least the lower part of the Grampian group represents sedimentation during the Grenvillian–Morarian interval, and that its rocks were affected first by the Morarian event, and subsequently by the Caledonian orogeny. These rocks are referred to informally as being of Morarian age.

This model poses the problem of a Morarian–Caledonian interval, the nature of which remains unresolved. The metasediments of the uppermost part of the Grampian group are reported to pass into the overlying Dalradian by a sedimentary transition^{3,10,11}, whereas in some areas tectonic contacts intervene between the two^{2,7,12}. Apart from sections near its tectonic base⁷ and others adjacent to the Dalradian^{3,10,11}, much of the Grampian group still awaits detailed examination. It may be significant that in the Grampian group west of Loch Erich, Thomas¹³ reports the presence of an older and a younger series of metasediments separated by a major slide.

West of the Great Glen Fault, in the Loch Eil Division^{1,2}, the rocks along and to the south of Loch Eil appear to closely match certain formations of the Grampian group in their lithologies, sedimentary structures and in their apparent degree of structural–metamorphic complexity. In the region of Glen Tarbert, the rocks match those of the Central Highland Division^{7,14}.

Nearer to the Moine Thrust, a case has been made for a Grenvillian age for the early metamorphism and deformation in the Morar Division^{15,16}. However, there is now mounting evidence^{5,14} that the Precambrian event in these rocks may have been the Morarian event, and that they may be broadly equivalent in age to the Torridonian sediments deposited on the foreland between 1,000 and 800 Myr (ref. 17)—a long standing correlation¹⁸. This Morar Division is separated from the almost certainly Grenvillian (see ref. 6) rocks of the Glenfinnan Division by a major break, the Sgurr Beag Slide (Fig. 1). If the Morar Division is indeed of Morarian age, then the Sgurr Beag Slide assumes a similar structural position in separating Grenvillian basement from Morarian cover, as the Grampian Slide east of the Great Glen Fault.

The lower part (at least) of the Grampian group, probably parts of the Loch Eil Division, the Morar Division, the Tarskavaig Moines (Fig. 1)—already correlated with the Torridonian Sleat Group¹⁷—and the rocks of the north-east Ox Mountains and Lough Derg inliers of Ireland, may all form parts of one major assemblage, to which the arkosic Torridonian of the foreland would also belong. Such an assemblage is regarded as being analogous to a combination of groups which, as has yet to be demonstrated in the field, may make up a Moine Supergroup of Morarian age.

M. A. J. PIASECKI

Department of Geology,
University of Hull,
Hull, UK

OTTO VAN BREEMEN

Scottish Universities Research and Reactor Centre,
East Kilbride,
Glasgow, UK

Received 31 January; accepted 1 March 1979.

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A Caledonian blueschist from the Irish Dalradian

THE occurrence of the blue amphiboles glaucophane and crossite in metamorphosed basic rocks is characteristic of terrains metamorphosed at high pressures. Most examples are from relatively recent fold belts. We record here a Caledonian blueschist from the Dalradian Supergroup in South Achill Island, County Mayo (Fig. 1). It is the first 'old' blueschist from Britain to occur in a regularly bedded and folded sequence and may imply an early high pressure metamorphic event in this part of the Dalradian, evidence for which was generally destroyed by either erosion or later metamorphism.

The blueschist outcrops on Claggan Beach, 0.75 km south-west of Ashleam Bay (Fig. 1). The rocks exposed on the beach are mostly metasediments. Psammites predominate on the north side with interbedded pelitic schists, while metabasites occur on the south side. The metabasites are predominantly albite–epidote–chlorite schists but contain epidosite pods a few tens of cm in diameter and a more continuous boudinaged epidosite layer about 1 m thick that contains crossite and is therefore referred to as a blueschist.

The geology of the area has been described elsewhere^{1–3}. The basic rocks have been ascribed to the Upper Dalradian by Harris and Pitcher⁴ but a Middle Dalradian age has been recently proposed by Max and Long⁵.

The blueschist is fine grained (0.1–0.2 mm) and predominantly composed of epidote that is typically near $\text{Ca}_{2.08}\text{Fe}_{1.01}\text{Al}_{2.12}\text{Si}_{3.11}$ (calculated from microprobe analyses on an anhydrous basis) but with up to 2.30 Al atoms at some analysed points. Crossite occurs throughout the rock but is also concentrated into thin layers visible in hand specimens. Crossite compositions range from $\text{Na}_{1.88}\text{Ca}_{0.15}\text{Fe}_{2.02}^{\text{tot}}\text{Mg}_{2.28}\text{Al}_{0.80}\text{Si}_{8.20}$ to $\text{Na}_{1.92}\text{Ca}_{0.07}\text{Fe}_{1.51}^{\text{tot}}\text{Mg}_{2.12}\text{Al}_{1.36}\text{Si}_{8.15}$, tending to be richer in glaucophane at the margins. The rock also contains quartz, albite (>99% Ab) and hematite, with small granules of sphene sometimes associated with the hematite. Quartz and albite tend to occur together in felsic segregations, and crossite occurs both with these phases and in regions of epidote only.

Crossite grains often show marginal alteration to finer grained amphiboles, especially where quartz, albite and hematite are also present. Crossites enclosed in epidote are often unaltered. Two distinct alteration products are recognised, but there may be some gradation between them. They are a bright green barrositic amphibole which usually replaces crossite directly, and a colourless to pale green actinolite that may mantle either the crossite or the barrosite. Microprobe analysis of these alteration products is difficult because of their fine grain size, but the barrosite in particular seems to be of rather variable composition. One point gave $\text{Na}_{1.54}\text{K}_{0.02}\text{Ca}_{0.65}\text{Fe}_{2.06}^{\text{tot}}\text{Mg}_{2.30}$.

Mn_{0.02} Al_{1.18} Ti_{0.01} Si_{7.69}. The actinolite is rich in Na and Al, near Na_{0.47} Ca_{1.55} Fe^{tot}_{1.49} Mg_{3.29} Mn_{0.01} Al_{0.70} Ti_{0.02} Si_{7.67}.

Crossite has not been found in separate smaller epidosite pods on the same beach, but the barroisitic and actinolitic amphiboles are both present and show similar mutual relationships. Stilpnomelane is also present in some of these smaller pods. We infer from these observations that crossite formed early in the metamorphic history of the rock and subsequently became unstable.

Crossite schists of this type are typical of many high pressure metamorphic belts throughout the world⁶ and, in the absence of jadeite and lawsonite, are probably best assigned to a high pressure greenschist sub-facies rather than the glaucophane schist facies. In such terrains the blue amphibole occurs in oxidised metabasites only and this may partly explain its scarcity in the Dalradian.

The Claggan blueschist we describe here is the first to be reported from the Dalradian and it is also the first from the British Caledonides to occur in a regularly bedded and folded sequence; the similar crossite schists at Ballantrae and Anglesey are isolated occurrences in areas of complex, highly faulted geology. It therefore seems that at least this part of the Dalradian underwent an early high pressure metamorphism and the observed breakdown of crossite may reflect a change in conditions towards a conventional Barrovian facies series. The Barrovian regional metamorphic grade in South Achill is very low¹ and it is therefore the most likely part of the Irish Dalradian for early assemblages to be preserved.

Ernst⁷ has documented the variations in blueschist abundances with age and suggests that the scarcity of pre-Mesozoic

blueschists results from changes in the thickness of lithospheric plates with time. Modern blueschist facies assemblages with jadeite, lawsonite or aragonite may not have been stable in the Palaeozoic Earth. However, blueschists may have formed in the past but have been particularly susceptible to destruction during orogeny. England and Richardson⁸ calculate that blueschists will tend to be rather rapidly destroyed by erosion after orogeny. Thus they interpret the scarcity of old blueschists as resulting from the destruction of blueschist belts which were once present. In addition, relaxation of the thermal gradient might destroy high pressure assemblages that remained at depth. The discovery of a crossite schist in the Dalradian may accord with both these theories, but it does provide evidence that traces of former high pressure metamorphism can be very largely destroyed.

Thus in South Achill the moderately high pressure crossite schists, formed early in the Grampian orogeny, were largely destroyed by subsequent metamorphism. It is possible that other blueschists formed from Dalradian and related rocks were uplifted and destroyed by erosion rather than further metamorphism. The evidence for this is the presence of detrital ferroglaucophane and crossite in probable mid-Ordovician rocks of the Longford-Down region recently reported by Sanders and Morris⁹.

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J. R. GRAY

B. W. D. YARDLEY

*School of Environmental Sciences,
University of East Anglia,
Norwich, UK*

Received 22 January; accepted 1 March 1979.

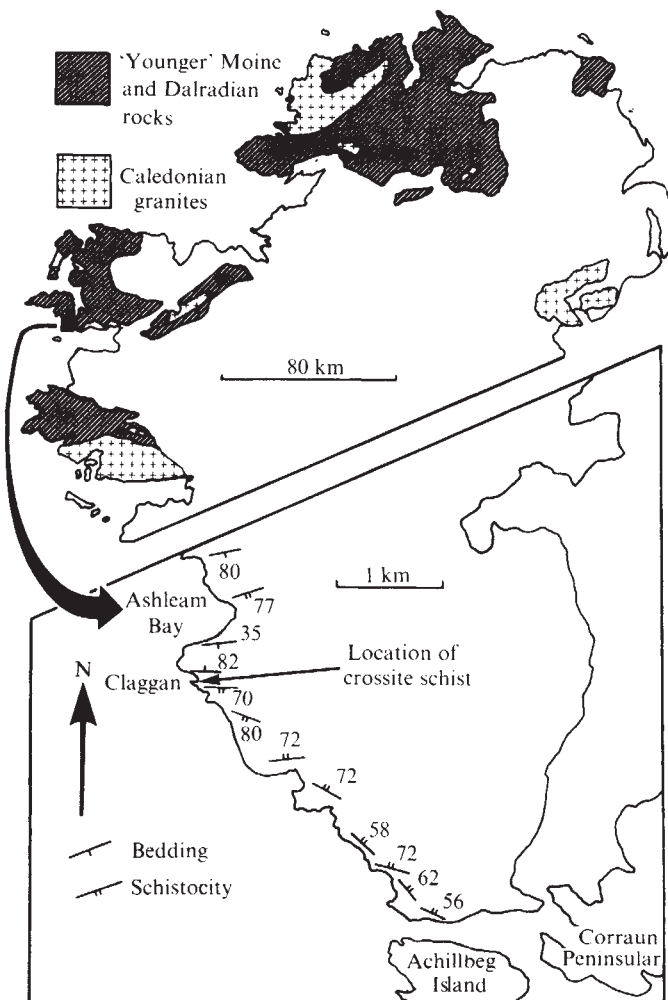


Fig. 1 Map showing the location of the blueschist occurrence in relation to the 'younger' Moine and Dalradian rocks of Ireland.

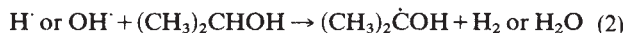
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Direct observation of a free radical interaction between vitamin E and vitamin C

VITAMIN E (α -tocopherol) and vitamin C (ascorbic acid) react rapidly with organic free radicals, and it is widely accepted that the antioxidant properties of these compounds are responsible in part for their biological activity¹⁻⁵. Tissue vitamin C levels are often considerably greater than those of vitamin E, for example in liver the values are approximately 2 mM and 0.02 mM, respectively. Nevertheless, vitamin E is considerably more lipophilic than vitamin C, and in biomembranes has been found to be the more potent antioxidant, particularly with respect to lipid peroxidation; penetration to a precise site in the membrane may be an important feature of the protection against highly reactive radicals⁶. Tappel has suggested that the two vitamins act synergistically, vitamin E acting as the primary antioxidant and the resulting vitamin E radical then reacting with vitamin C to regenerate vitamin E⁷. We now report direct observation of this interaction, which we feel may be an important feature in the maintenance of vitamin E levels in tissues.

As vitamin E is poorly soluble in water, conventional pulse radiolysis techniques, involving aqueous solutions and oxidising radicals such as $\text{OH}^\cdot$, cannot be used to generate the related free radical (Vit E $^\cdot$). We have shown that the trichloromethylperoxy radical $\text{Cl}_3\text{COO}^\cdot$ can be generated in aerated water-isopropanol-acetone mixtures containing carbon tetrachloride,

reactions (1)–(5). The radical is a moderately reactive one-electron oxidising agent and has been shown to react with various nucleophilic compounds, with rate constants of the order of 10^7 – 10^8 $\text{M}^{-1} \text{s}^{-1}$ (ref. 8).



On pulse radiolysis of such a solution containing vitamin E we have observed the formation of a transient species with an absorption spectrum similar to those previously assigned to phenoxy radicals⁹. We attribute the absorption to the radical, Vit E[•]. Free radical scavenging actions by vitamin E have been ascribed to the initial reaction of the phenolic hydroxyl group with the production of a phenoxy radical¹¹. The rate of its formation was first order in vitamin E concentration corresponding to:



$$k = 5 \pm 1 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$$

The absorption decayed over a period of 3 ms. However, in the presence of vitamin C its spectrum changed rapidly, a decrease in absorption at 425 nm occurring simultaneously with an increase at 360 nm. These changes are attributed to the formation of the vitamin C radical (Vit C[•]) in view of previously published data concerning its absorption spectrum^{2–4}:

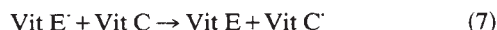


Figure 1 shows spectra of the transient species present 10 μs , 400 μs and 1,600 μs after an aerated solution containing isopropanol (50%), acetone (10%), carbon tetrachloride (0.04 M), α -tocopherol (3.4×10^{-3} M) and ascorbic acid (1.60×10^{-3} M) neutralised with sodium hydroxide was irradiated with a 0.2- μs pulse of 4 MeV electrons from the Brunel linear accelerator.

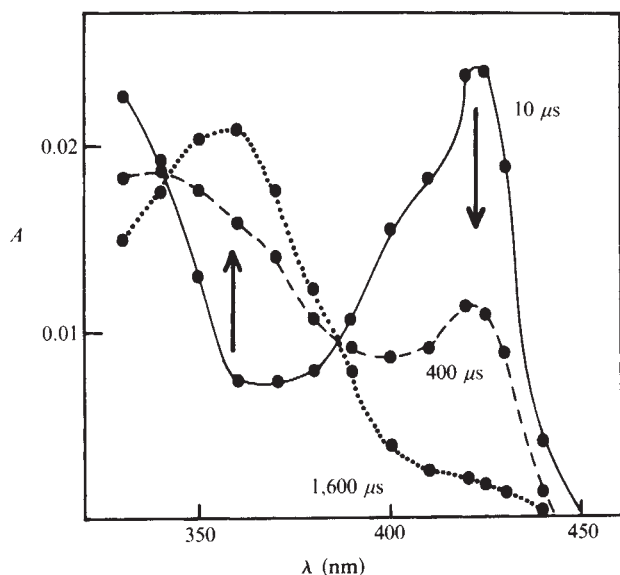


Fig. 1 Absorption spectra at various times after pulse radiolysis of an aerated solution of vitamin E and vitamin C. (—●—) vitamin E[•], (·····) vitamin C[•]; see text.

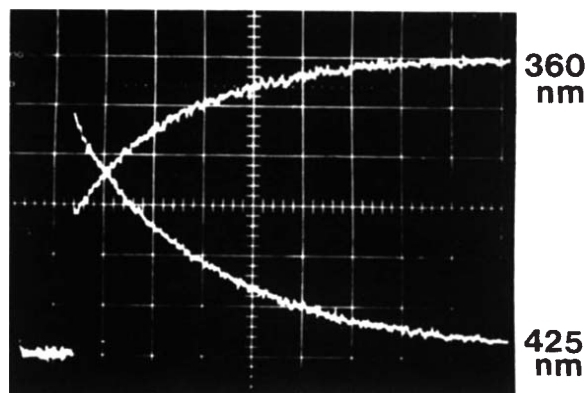
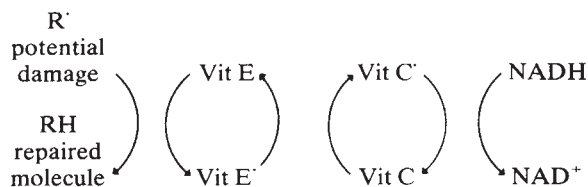


Fig. 2 Oscilloscope traces obtained at 425 nm (decay of vitamin E[•]) and at 360 nm (grow-in of vitamin C[•]) for the reaction between the vitamin E radical and vitamin C (2.88×10^{-3} M ascorbate). Ordinate, 1% absorption per large division; abscissa, 100 μs per large division.

After 10 μs the spectrum is principally that of Vit E[•] with a small contribution (10%) from Vit C[•] whereas after 1,600 μs the spectrum is that of Vit C[•] alone. Oscilloscope traces of the decay of Vit E[•] at 425 nm and the concurrent grow-in of Vit C[•] at 360 nm are shown in Fig. 2 for a similar solution but containing 3.2×10^{-3} M ascorbic acid. Both the decay and the formation of the absorbing species were exponential, with first order rate constants proportional to vitamin C concentration. From measurements at four vitamin C concentrations the rate constant for reaction (7) was $1.55 \pm 0.2 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$.

Such a rapid interaction may well be pertinent to protection from free radical-mediated damage *in vivo*: the recycling of vitamin E at the expense of vitamin C may account in part for the fact that clinically overt vitamin E deficiency has not been demonstrated in man. Moreover in certain conditions the vitamin C radical can itself be enzymatically reduced back to vitamin C by a NADH-dependent system¹⁰. Thus this allows the repair of an otherwise potentially damaging organic free radical R[•] to be linked to NADH oxidation and a wide range of normal biochemical processes.



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J. E. PACKER
T. F. SLATER
R. L. WILLSON

Biochemistry Department,
Brunel University,
Uxbridge, UK

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Opposite cerebral hemispheric superiorities for visual associative processing of emotional facial expressions and objects

STUDIES of patients with unilateral cerebral lesions¹ or surgically disconnected hemispheres² suggest a functional asymmetry in processing visual information by the two hemispheres. The right hemisphere (RH) seems to favour matching of pictures of objects by similarity of shape (apperceptive matching), whereas the left hemisphere (LH) favours matching by similarity of meaning or conceptual category (associative matching). As, on the other hand, considerable recent experimental evidence supports the hypothesis that the RH might have a distinct role in processing emotional information³⁻⁸, it would be surprising if the RH lacked the capacity of associative processing which is important in emotional communication. Using tachistoscopic half-field presentation the present study produces evidence for a RH superiority for associative processing in response to adequate stimuli such as emotional facial expressions, whereas the LH is more efficient in detecting similarity of function between objects whose shapes are very different.

Twenty-four adult right-handed normal subjects (12 men, 12 women, 20-30 yr old) performed two visual half-field experiments. The method was identical in both experiments. Subjects had to fixate a central point in a two-channel tachistoscope. Two pictures were then simultaneously shown to them for 150 ms. One of the pictures, a stylised drawing, was always presented in central vision at the point of fixation. The other, a photograph, was presented to either the left or the right side of the drawing, either in the left or the right visual field (LVF/RVF). With exposure a timer was started. If the subject felt that the two pictures represented the same meaning, he pressed a button to stop the timer, otherwise no response had to be given. Equal numbers of positive and negative instances were presented randomly and equal runs of right and left hand responses were used in alternation. Each subject participated in four sessions, on four different days. A session consisted of 96 projections for each experiment. A total of 384 pairs of pictures per subject and experiment were shown.

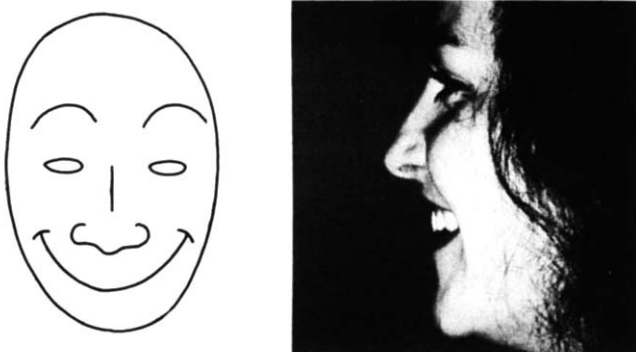


Fig. 1 'Happy', an example of a common emotional expression in two faces of different shape. The faces were photographed as close as possible according to the features outlined by Ekman and Friesen⁹. To enhance affectivity, the two persons whose faces were photographed were known to all subjects. The stylised drawing was always presented in central vision, subtended a maximum visual angle of 1.7° on each side of the point of fixation. The photograph of the same size was presented either on the left or the right side of the drawing, within $2.2-5.6^\circ$ of visual angle from fixation point. The 24 subjects were subdivided into two groups of 12 (6 men, 6 women) to whom photographs were presented with faces or objects orientated to the right or the left respectively. The order of presentation was alternated between the experiments, balanced for sex of subjects and picture orientation.

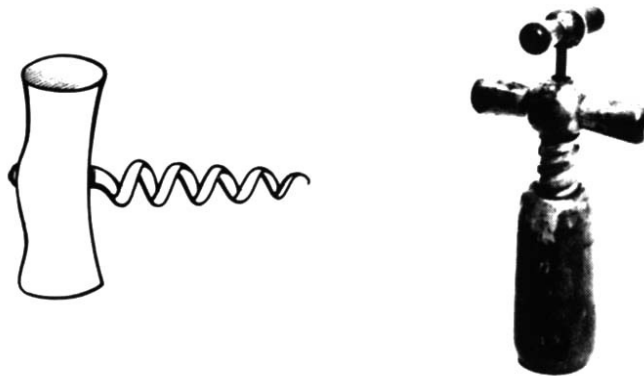


Fig. 2 'Corkscrew', an example of a common category to which two different objects belong.

In experiment 1, subjects were presented with pairs of pictures, one representing a stylised drawing of an emotional facial expression in front view, the other a photograph of a male or female face in profile, showing the same or a different emotional facial expression, that is, 'happy' (Fig. 1), 'angry' or 'astonished'. All possible combinations of the three drawings and six photographs were used. Variance analysis of times of correct decisions revealed faster times for LVF than for RVF ($F(1.368) = 15.72$; $P < 0.001$), indicating RH superiority (Fig. 3) and a significant decrease in time in the course of the testing ($F(3.368) = 6.44$; $P < 0.001$), suggesting a 'learning effect'. Differences between hands and interactions did not differ significantly ($P > 0.05$). Neither the sex of the person being tested nor the orientation of faces on the photographs had any significant influence on the difference in times of decision between visual fields. There were 24% errors. Analysis of errors revealed a significant decrease in the course of the testing, independent of visual fields ($F(1.6) = 27.47$; $P < 0.005$). No other differences in errors between visual fields, hands, sex of subjects or orientation of pictures could be found.

In experiment 2, presentation and data analysis were identical to those in experiment 1. Drawings and photographs represented three different categories of objects, that is 'corkscrew' (Fig. 2), 'key' and 'brush'. Times for correct decisions were shorter for RVF than for LVF ($F(1.368) = 11.31$; $P < 0.001$), indicating LH superiority (Fig. 3) and the learning effect was again significant ($F(3.368) = 10.72$; $P < 0.001$). Again there was no significant difference in times of decision between hands and interactions. Neither the sex of subjects nor the orientation of objects on the photographs had an influence on the difference in time between the visual fields. There were 4% errors equally distributed between visual fields, hands, sex of subject and orientation of pictures. No decrease in errors in the course of testing could be found.

The above findings show that associative processing of non-verbal visual information is stimulus dependent and that there is a functional asymmetry of associative processing by the two hemispheres. A possible mechanism, which would very probably favour the LH, could be 'inner verbalisation'. To reduce possible differences in the capability of verbalisation, we used as a reference picture a highly stylised drawing, which allowed easy verbalisation of the emotional facial expression as well as of the object classes. Nevertheless the behaviour of the subjects indicated very different levels of awareness of the correctness of decisions for emotional facial expressions as opposed to object categories. Often, erroneous object judgments were followed by rapid recognition of the errors, whereas for emotional expressions subjects repeatedly expressed the sense of having made an error, when in fact the manual response had been correct. However this is an incidental observation which needs to be explored systematically.

To conclude, we found that visual associative processing is not exclusively a function of the left hemisphere, but that both

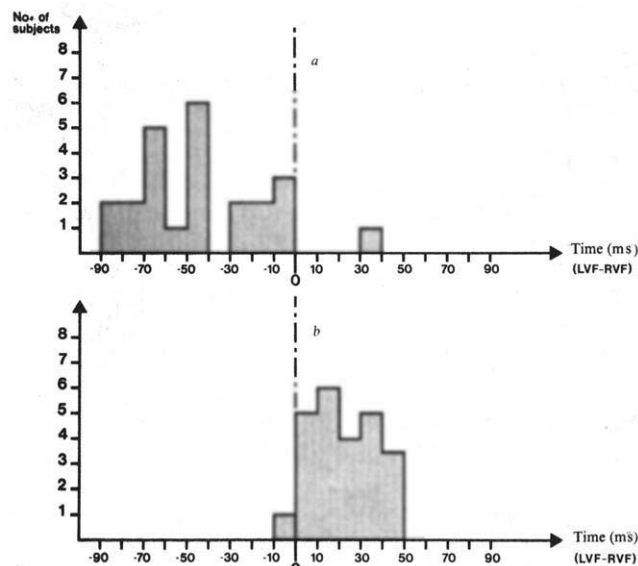


Fig. 3 Distribution of the subjects with respect to the mean differences of decision times (ms) between the left and the right visual field (LVF-RVF), that is, negative differences represent faster decision times in LVF, thus indicating right hemisphere superiority. *a*, Experiment 1 (emotional expression); *b*, experiment 2 (object).

hemispheres are capable of visual associative performance. There are, however, two different associative procedures: The left hemisphere seems to be superior on an associative task requiring recognition of a common category to which different objects belong, whereas the right hemisphere seems to be superior on an associative visual task requiring recognition of a common emotional facial expression in different faces. Although it is not proven that the emotional feature in the facial expression was critical in producing the right hemisphere superiority, this would be consistent with the recently expressed view, that the RH might have a distinct role in processing emotional information.

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THEODOR LANDIS

*Aphasia Research Center,
Boston Veteran's Administration Hospital,
Boston, Massachusetts 02130*

GIL ASSAL

*Institute of Neuropsychology,
Neurosurgical Clinic,
CHUV, Lausanne, Switzerland*

ETIENNE PERRET

*Institute of Neuropsychology,
Neurological Clinic,
University Hospital Zurich, Switzerland*

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Naloxone dose dependently produces analgesia and hyperalgesia in postoperative pain

If endorphins modulate pain, then naloxone should affect pain behaviour even in subjects who have not received exogenous opiates. However, some naloxone studies claim a lack of effect^{1,2}, others a hyperalgesic effect³⁻⁵, and others both hyperalgesic and analgesic effects^{6,7}. Such discrepancies may arise from the different methods used to induce and assess pain⁸, and from variation in dose. We know of only one previous human study which used multiple doses of naloxone⁶; this indicated a dose-dependent bi-directional effect. In the present study, a clinical pain paradigm was used to generate a dose-response curve for naloxone. We report that naloxone produces analgesia at low doses and hyperalgesia at high doses.

The patients studied were 35 males and 42 females, aged 19-32 yr. Detailed methods were published previously⁸. Subjects underwent a standardised surgical procedure for the removal of impacted mandibular third molars after premedication with 10-20 mg of diazepam. During surgery, 15-40% nitrous oxide and local anaesthesia with 3% mepivacaine without vasoconstriction (effective duration 45-75 min, ensuring reversal of anaesthesia before experimental interventions) were used. Naloxone can have effects which are not specific for opiates. In fact, a naloxone interaction with both diazepam^{9,10} and nitrous oxide¹¹ has been reported. However, these interactions are unlikely to have a significant effect on the conclusions of this study for reasons discussed previously⁸.

The patients received placebo as their first medication 2 h after the onset of local anaesthesia. One hour later, naloxone was given double blind in doses of 0 (placebo), 0.4, 2, 7.5 or 10 mg. Patients rated their pain by a mark on a 10-cm horizontal line which had the words 'no pain' at the left (0 cm) end and 'worst pain ever' at the right (10 cm). The validity of this scale has been discussed elsewhere⁸. Pain was measured 5, 20 and 60 min after each injection. The pain at 60 min, the time of greatest placebo effect, was used in the present analysis. Pain, with this paradigm, increases over time. This was demonstrated by administration of placebo by a secret intravenous infusion line so that the patients did not know that they had received anything, and the surgeon did not know what he had administered (a blind placebo)¹². Placebo responders were those subjects in whom pain decreased or was unchanged 1 h after placebo administration. Placebo non-responders were those patients whose pain increased over that hour.

Figure 1 shows dose-response curves for the change in pain and mean pain levels, 1 h after naloxone. For placebo responders, the dose-response curve is bi-directional. Compared with placebo, naloxone at low doses (0.4 and 2 mg) produces analgesia, whereas at higher doses (7.5 and 10 mg) it produces hyperalgesia. The naloxone-induced reduction in pain level is significantly greater than that produced by placebo both at the 0.04 mg dose ($0.01 > P > 0.005$, by the Student *t* test) and at the 2 mg dose ($0.05 > P > 0.025$) of naloxone. At the 7.5 and 10 mg doses, the change in pain is significantly greater than that produced by placebo ($0.05 > P > 0.025$). Figure 1*b* also demonstrates a bi-directional dose-response curve when pain level, rather than change in pain, is plotted.

When the analysis is carried out for placebo non-responders, naloxone has relatively little effect (Fig. 1*a*). In fact, if all non-responders are compared with placebo (0 mg), there is a slight hyperalgesia ($0.1 > P > 0.05$). When responders and non-responders are pooled, the bi-directionality is still apparent (Fig. 1*a*).

The finding that naloxone has a bi-directional dose-response curve present in placebo responders, may resolve some of the apparent conflict among previous reports. Grevert and

Goldstein¹, k 1 and 10 mg naloxone, and El-Sobky *et al.*², using 0.4 and 0.8 mg, found no effect in opiate-naïve humans. Both used experimental rather than clinical pain, and combined placebo-responding and non-responding populations. Buchsbaum *et al.*⁷ also used experimental pain, but they divided subjects into 'pain-sensitive' and 'pain-insensitive' groups, according to their rating of an electric shock. They found that 2 mg of naloxone (a dose we found to be analgesic in placebo responders) produced only analgesia in pain-sensitive subjects. Perhaps the use of clinical pain or the segregation of patients is necessary to show consistent naloxone effects.

In animal studies using various tests for pain, only hyperalgesic actions have been reported, even when very low doses of naloxone (0.01 mg per kg in mouse) are used^{3-5,13,14}. Naloxone hyperalgesia is stereospecific^{15,16}, and thus probably represents specific opiate receptor blockade. Analgesia is one of the major opiate agonist effects; thus, the finding that the opiate antagonist naloxone produces analgesia at low doses is unexpected. It is interesting that this apparent agonist action is only observed in humans. Naloxone has no other reported agonist effects^{3-5,13,14,17-20}.

There are several possible explanations for naloxone-induced analgesia. The analgesia could be mediated through a non-opiate system (that is, a nonspecific effect); naloxone could have previously unsuspected agonist activity, or could produce analgesia indirectly by specific antagonist actions. It is unlikely that

naloxone analgesia is a nonspecific effect, first, because analgesia is only seen in placebo responders, and second, because it is produced only by lower doses of naloxone.

Naloxone might have an agonist action. Because of the extensive pharmacological evidence that naloxone is a pure antagonist, the analgesia and hyperalgesia would have to be produced at separate and perhaps pharmacologically distinct receptor sites. Although there is evidence for several distinct opiate receptors in mammalian brain^{18,20}, naloxone has not been shown to have an agonist effect on any of them.

Another possibility is that naloxone produces analgesia indirectly. If low-dose naloxone elicits release of endorphins, or perhaps displaces endorphins from receptor sites not relevant to analgesia^{21,22}, whereas at higher doses it blocks the action of the released or displaced endorphin at the postsynaptic receptor for analgesia, the dose-response curve would have a bi-directional characteristic. In a previous paper²³ and in the present study (Fig. 1b), we observed that naloxone in high doses (10 mg) exactly cancels the placebo response; that is, it brings the mean pain of the responders to that of non-responders. One interpretation is that only in placebo responders are endorphins released, and thus low-dose naloxone only produces analgesia in placebo responders.

This hypothesis assumes that low doses of naloxone are insufficient to block the analgesic effect of the endorphin that is released. This assumption is consistent with clinical studies using naloxone postoperatively to reverse narcotic anaesthesia. Low doses (1–2 µg per kg) of naloxone, which reverse respiratory and mental depression from opiates, do not reverse analgesia²⁴⁻²⁶. Thus, a higher dose of naloxone is required to block analgesia than to block other agonist actions. When these higher doses are given, relative hyperalgesia is produced. This is also supported by studies which demonstrate a low affinity of morphine relative to endorphins for brain opiate receptors²⁷.

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JON D. LEVINE
NEWTON C. GORDON
HOWARD L. FIELDS

Departments of Neurology, Physiology,
and Oral Medicine,
University of California,
San Francisco, California 94143

Received 2 November 1978; accepted 20 February 1979.

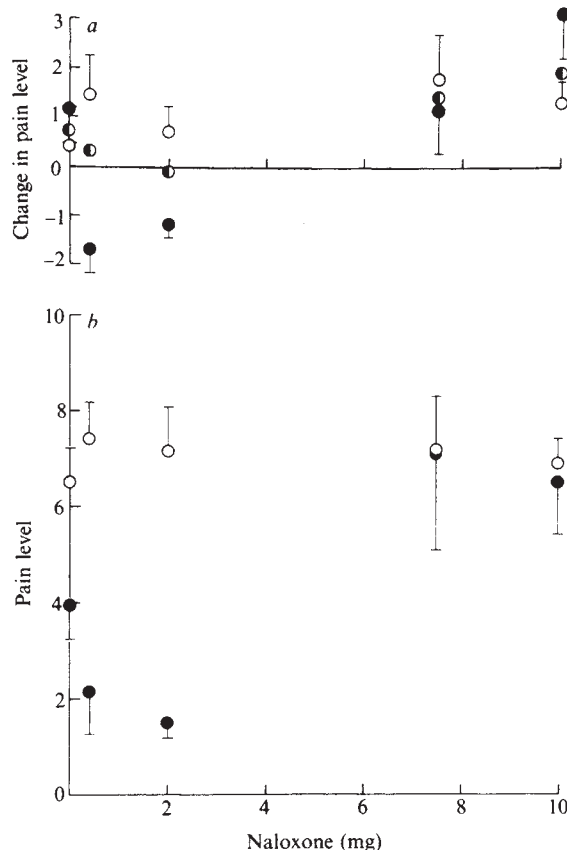


Fig. 1 Dose-response curve for the effect of naloxone on post-operative pain. The change in pain level (a) and the mean pain level (b), with standard error bars, 1 h after different doses of naloxone, is plotted for the three groups of patients: (1), placebo responders (●); (2), placebo non-responders (○); (3), groups (1) and (2) pooled (●●). Sample sizes for responders and non-responders, respectively, are: 7 and 13 (0 mg); 5 and 10 (0.4 mg); 4 and 6 (2 mg); 6 and 6 (7.5 mg); 7 and 13 (10 mg). The increase in pain following a second placebo (change in pain for responders given 0 mg) represents transition to non-responders in some patients who were responders to the initial placebo, administered 1 h before administration of the dose plotted.

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Antiviral effect of interferon *in vivo* may be mediated by the host

INTERFERON has antiviral effects both *in vivo* and *in vitro*. Viral replication is inhibited in interferon-treated cells *in vitro* because the reproductive cycle of the virus is inhibited at the transcriptional or translational level, depending on the virus-cell system studied¹. This direct inhibition of viral replication has been assumed to also be the mechanism by which interferon exerts its antiviral effect *in vivo*. We report here results that indicate protection by interferon against viral infection *in vivo* without inhibition of the viral replication of the same virus *in vitro*.

To test the antiviral effect of human leukocyte interferon (HLI) *in vivo*, six rhesus monkeys were infected intradermally with different doses of vaccinia virus (strain of the Rijks Instituut voor de Volksgezondheid, RIV)² of which three were treated daily with HLI administered intramuscularly. The HLI was prepared as described previously³. The preparation used in these experiments had a specific activity of 2.1×10^6 units per mg protein. In control monkeys the lesions reached their maximum at day 7. Daily intramuscular injections of 5×10^5 units HLI per kg body weight during 8 d completely inhibited the development of the typical vaccinia-induced skin lesions (Fig. 1). No skin lesions were detected during the observation period of 4 weeks following infection. However, we were unable to correlate this distinct *in vivo* effect of HLI with a corresponding inhibition of the cytopathogenic effect (CPE) of the same virus on diploid rhesus monkey skin fibroblasts or on Rous sarcoma virus transformed human fibroblasts (RSb cells). Up to 10^4 units of HLI failed to protect the cells against the CPE of vaccinia virus (RIV strain), although the CPE of vesicular stomatitis virus (VSV) was effectively inhibited (Table 1). Surprisingly, vaccinia virus was resistant to interferon in our *in vitro* system, but the same results were obtained *in vitro* with the vaccinia virus strain WR and with smaller challenge doses (10^{-3} TCID₅₀)⁴. Also no anti-vaccinia activity could be detected in the sera of the monkeys 4 h after the first injection with HLI. At this time, the sera showed the maximum titre of antiviral activity when tested against VSV. Similar experiments performed with human diploid skin fibro-

Table 1 *In vitro* inhibition of the cytopathogenic effect (CPE) of vaccinia virus by human leukocyte interferon (HLI) and serum from rhesus monkeys treated with HLI

Preparation	RSb cells		Skin fibroblasts from rhesus monkeys	
	VSV	Vaccinia virus	VSV	Vaccinia virus
HLI, 10^4 units ml ⁻¹	10,000	<1	10,000	<1
Pre-serum*	<10†	<10	ND	ND
Post-serum*	350†	<10	ND	ND

Rous sarcoma virus transformed human fibroblasts (RSb) or monkey skin fibroblasts were plated in microtitre plates, grown to confluency (4×10^4 cells per well) and treated with serial dilutions of HLI containing 10^4 units per ml of rhesus monkey sera (before and after injection of 5×10^5 units HLI kg⁻¹). After overnight incubation, the supernatant was removed and cells were infected with vesicular stomatitis virus (VSV) or vaccinia virus (multiplicity of infection 0.25 TCID₅₀ per cell). The incubation was terminated when untreated infected control cells showed more than 90% CPE. The cells were stained with crystal violet. Both viruses were always tested simultaneously in the same microtitre plate and an interferon standard preparation was included. The activity of interferon is expressed as the reciprocal of the highest dilution giving 50% protection. The titres are given as reference units (tested against standard preparation 69/19).

* Before and after 4 h after injection of rhesus monkeys with 5×10^5 units of HLI per kg.

† Mean titre of three monkeys. ND, not determined.

blasts and rhesus monkey kidney cells showed identical results. There was also no inhibition of the production of infectious vaccinia virus (unpublished results).

These findings indicate that interferon can be effective *in vivo* against a virus which is insensitive to its antiviral action in various cell types. Likewise, it has been shown by others⁵ that interferon can inhibit *in vivo* the growth of tumour cells which are resistant to its growth inhibitory action *in vitro*. Interferon may activate several defence systems of the host, for example, the cytotoxicity of the natural killer cells and the macrophages^{6,7}. Perhaps such 'aggressive' cells can selectively destroy virus-infected cells *in vivo*.

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H. SCHELLEKENS

Department of Virology,
Erasmus University,
PO Box 1738, Rotterdam

W. WEIMAR

Department of Internal Medicine,
Erasmus University,
Rotterdam, The Netherlands

K. CANTELL

State Serum Institute,
Helsinki,
Mannerheimintie 166, Finland

L. STITZ

Primate Center TNO,
Virology Section,
151, Lange Kleiweg,
2280 HV, Rijswijk, The Netherlands

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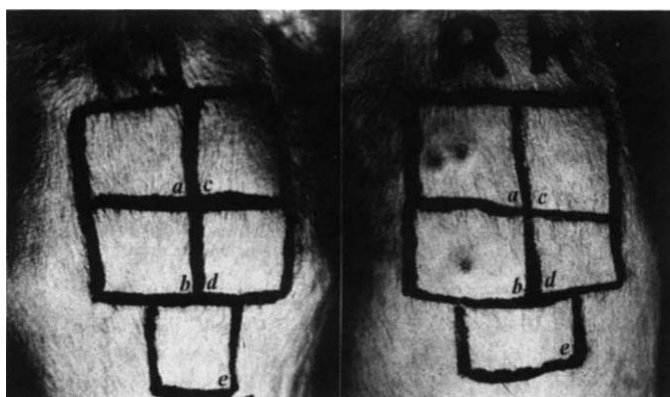


Fig. 1 *In vivo* effect of human leukocyte interferon (HLI) in rhesus monkeys infected intradermally with vaccinia virus. Monkeys were treated with HLI from day -1 to day 7 at 5×10^5 units kg⁻¹ i.m. They were vaccinated intradermally at day 0 with the following preparations: 10^7 TCID₅₀ ml⁻¹ vaccinia virus (a); 10^6 TCID₅₀ ml⁻¹ vaccinia virus (b); 10^5 TCID₅₀ ml⁻¹ vaccinia virus (c); 10^7 TCID₅₀ ml⁻¹ vaccinia virus, subjected to UV- and heat-inactivation (d); NaCl (e). For each dilution, 0.05 ml were injected at three sites. The vaccination sites 12 d after infection are shown in a rhesus monkey treated with HLI (left) and in a control monkey (right). Three monkeys were treated with interferon and three served as controls.

Thrombin and epidermal growth factor become linked to cell surface receptors during mitogenic stimulation

THERE is much evidence that interaction with specific cell surface receptors is a key event in the action of polypeptide hormones and growth factors. Many analyses of hormone-receptor interactions have been carried out based on the assumption that hormone binding to the cell receptors is a reversible reaction¹⁻³. Indeed, many studies have demonstrated that bound hormones dissociate from their receptors. However, in most systems the possibility could not be excluded that a significant fraction of the hormone molecules that bind to cells become linked to their receptors. Our present studies with the polypeptide mitogens ¹²⁵I-thrombin and ¹²⁵I-epidermal growth factor (¹²⁵I-EGF) show that a significant percentage of the

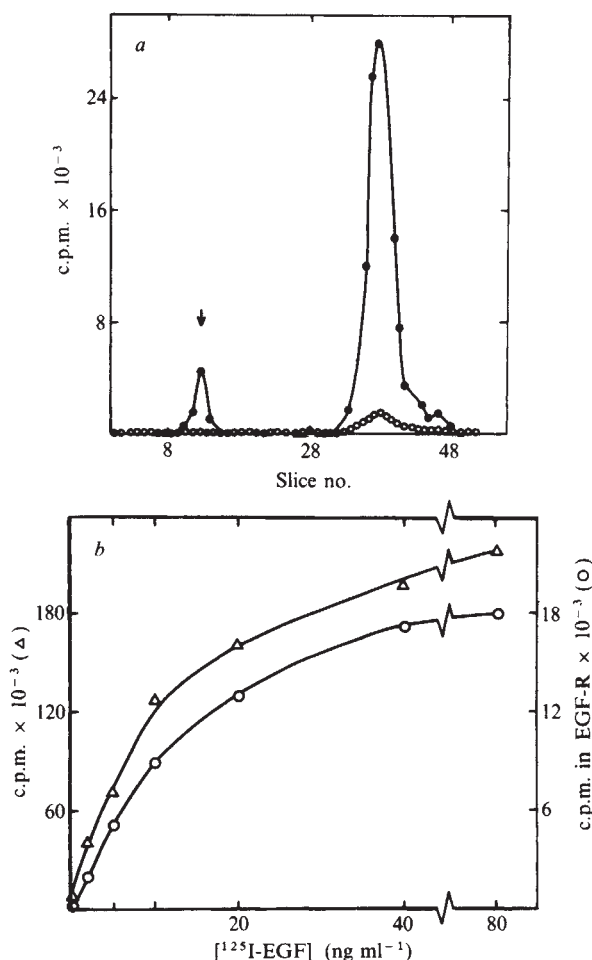


Fig. 1 Linkage of ¹²⁵I-EGF to cell receptors. *a*, Cultures were rinsed with DV medium containing 15 mM hydroxyethyl-*N,N'*-piperazine sulphonate, pH 7.3 (DV HEPES medium), and incubated for 1 h at 37 °C with 3 ml DV HEPES medium containing 0.1% bovine serum albumin (BSA) and either ¹²⁵I-EGF (10 ng ml⁻¹) (●) or ¹²⁵I-EGF plus 2 μg ml⁻¹ unlabelled EGF (○). The cultures were rinsed six times with 2 ml ice-cold phosphate-buffered saline (PBS) and the cells solubilised in 0.2 ml 0.1 M Tris buffer (pH 6.8) containing 3% SDS, 1% 2-mercaptoethanol, 2.0 mM phenylmethyl sulphonylfluoride and 0.6% *N*-ethylmaleimide. The samples were incubated in a boiling water bath for 5 min and applied to disc gels containing 5–20% linear polyacrylamide gradients and 0.1% SDS. The gels were cut into 2-mm slices, dried, and the radioactivity measured with a γ-counter. The arrow indicates the 170–190 K component. *b*, The experiment described in *a* was carried out using ¹²⁵I-EGF at the indicated concentrations. The radioactivity in the bands was corrected for nonspecific binding by subtracting the radioactivity bound in the presence of 2 μg ml⁻¹ unlabelled EGF. ○, c.p.m. in the 170–190 K component (EGF-R); Δ, total specifically bound radioactivity (c.p.m. in EGF-R plus c.p.m. in unlinked ¹²⁵I-EGF).

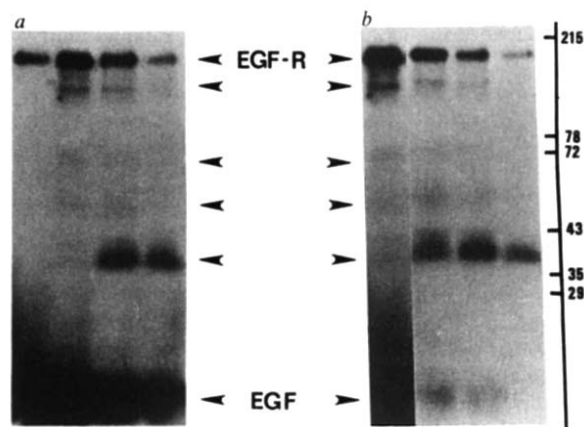


Fig. 2 Time courses of formation and degradation of EGF-R. *a*, As described in Fig. 1*a*, HF cells were incubated with ¹²⁵I-EGF (20 ng ml⁻¹) for various periods, rinsed, solubilised and heated. Samples (20 μl) and red blood cell marker proteins were applied to slab gels containing a 5–20% linear polyacrylamide gradient and 0.1% SDS. The gels were fixed, stained with Coomassie blue, and dried. Autoradiographs were produced using Kodak XOMAT R film. Lanes 1–4 show the results of incubating cells with ¹²⁵I-EGF for 10, 60, 180 and 420 min, respectively. *b*, HF cell cultures were incubated with ¹²⁵I-EGF (20 ng ml⁻¹) as described in Fig. 1*a*, and were quickly rinsed six times with ice-cold PBS. The cultures were reincubated at 37 °C with 3 ml DV HEPES medium for various periods. The cells were then rinsed twice with ice-cold PBS, solubilised and heated as described in Fig. 1*a*. SDS-PAGE and autoradiography were carried out as described in *a*. Lanes 1–4 show 0, 60, 120 and 180 min incubations, respectively, following removal of ¹²⁵I-EGF-containing medium.

molecules that are specifically bound on human fibroblasts become linked to cell surface receptors. This finding has broad implications for the way in which these molecules might stimulate cell division. It also raises the question of whether linkage of polypeptide hormones to their receptors is a general phenomenon.

Human foreskin (HF) cells (passage 7–11) were grown in Falcon tissue culture dishes containing Dulbecco–Vogt modified Eagle's medium (DV medium) and 5% calf serum as previously described⁴. Cells for experiments were seeded in 60-mm dishes at 3×10^4 cells per cm², and were incubated in serum-containing medium for 3 d, then in serum-free medium for 2 d. EGF was purified by the method of Savage and Cohen⁵. EGF⁶ and thrombin⁷ were iodinated by published procedures. Both proteins contained an average of 0.7 I-atoms per molecule. SDS-polyacrylamide gel electrophoresis (SDS-PAGE) using disc and slab gels was carried out by the method of Laemmli.⁸

We have recently used the procedures of Das and Fox to radiolabel the EGF receptors on HF cells with ¹²⁵I-EGF-NAPEDE, a photoactivable cross-linking derivative of ¹²⁵I-EGF⁹. We found that the EGF-receptor complex had a molecular weight (MW) similar to the 190,000 dalton (190 K) EGF-receptor complex reported in mouse cells¹⁰. During this work, we discovered that some of these receptors also became labelled by ¹²⁵I-EGF that lacked a photoactivable group. Figure 1*a* shows the distribution of radioactivity in gel slices after SDS-PAGE of solubilised HF cells that had been incubated with ¹²⁵I-EGF (10 ng ml⁻¹) for 60 min at 37 °C. In this and the following experiments, the cells were solubilised by boiling in 3% SDS and 1% 2-mercaptoethanol, conditions that disrupt noncovalent interactions between most proteins. As shown, about 90% of the radioactivity was found in a rapidly migrating band. We identified this material as ¹²⁵I-EGF on the basis of its MW (about 6,000). In addition, 6–9% of the radioactivity specifically bound to the cells was contained in a 170–190 K component. This component was absent when a vast excess of unlabelled EGF was present in the binding medium to reduce interaction of ¹²⁵I-EGF with its receptors (Fig. 1*a*), or when ¹²⁵I-EGF was incubated without cells. These results showed that a significant fraction of bound ¹²⁵I-EGF became directly linked to cellular receptors for EGF. This linkage was probably

covalent because the labelled 170–190 K component survived treatment with 6 M guanidine-HCl and 0.1 M 2-mercaptoethanol¹¹.

The amount of ¹²⁵I-EGF that became linked to receptors (EGF-R) increased with increasing concentrations of ¹²⁵I-EGF and was maximal at 40 ng ml⁻¹ ¹²⁵I-EGF (Fig. 1b). This was about the same concentration dependence displayed by total specific ¹²⁵I-EGF binding. Thus, at all ¹²⁵I-EGF concentrations examined, linked ¹²⁵I-EGF accounted for a relatively constant fraction (6–9%) of the total specifically bound ¹²⁵I-EGF. Also, the amount of EGF-R varied with duration of ¹²⁵I-EGF incubation roughly in parallel with total specific ¹²⁵I-EGF binding. Figure 2a (lane 1) shows that EGF-R and also ¹²⁵I-EGF specifically bound but not linked (EGF) were apparent after only 10 min incubation at 37 °C. The amounts of both EGF-R and EGF continued to increase during the first hour of incubation with ¹²⁵I-EGF (lane 2), but decreased markedly during the next few hours (lanes 3 and 4). The decrease in ¹²⁵I-EGF binding that occurs during several hours of incubation with ¹²⁵I-EGF is caused by a decrease in the number of EGF receptors (down regulation)^{12,13}. Apparently, the receptors that were linked to ¹²⁵I-EGF were down-regulated with the other EGF receptors.

The rate at which ¹²⁵I-EGF became linked to receptors suggested that this reaction took place at the cell surface. Consistent with this view, EGF-R formed during a 10-min incubation with ¹²⁵I-EGF was completely removed by a 10-min treatment with trypsin (10 µg ml⁻¹) at 37 °C. However, after a

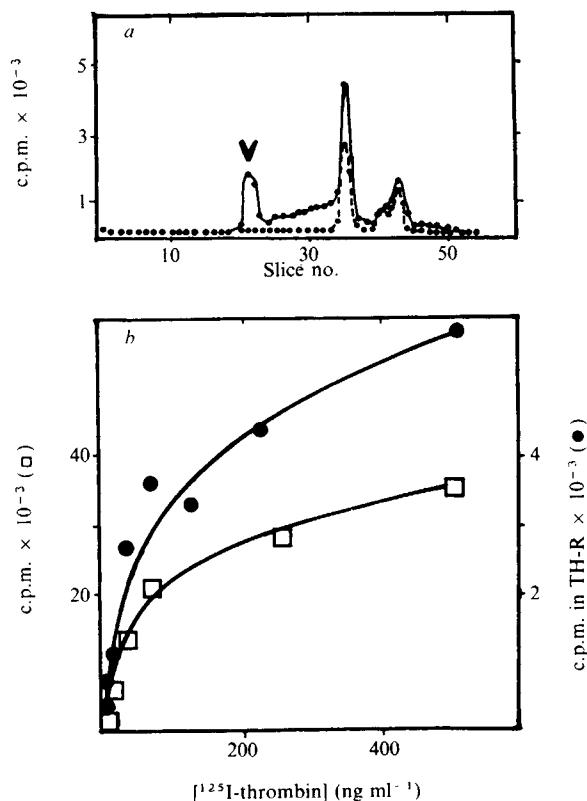


Fig. 3 Linkage of ¹²⁵I-thrombin to cell receptors. *a*, Cultures were incubated at 37 °C for 20 min with DV HEPES medium, and the medium was replaced with DV HEPES medium containing 0.5% BSA and either ¹²⁵I-thrombin (0.25 µg ml⁻¹) (●) or ¹²⁵I-thrombin plus 5 µg ml⁻¹ unlabelled thrombin (□). The cultures were then incubated for 90 min at 37 °C and rinsed, solubilised and heated as described in Fig. 1a. The samples were applied to disc gels containing 7.5–15% polyacrylamide linear gradients and 0.1% SDS. The radioactivity in gel slices was determined as described in Fig. 1a. The arrow indicates the 65K component. Unlinked ¹²⁵I-thrombin migrated in gel slices 34–37. *b*, The experiment described in *a* was carried out with ¹²⁵I-thrombin at the indicated concentrations. The radioactivity in the 65K and unlinked ¹²⁵I-thrombin bands were corrected for nonspecific binding by subtracting the radioactivity that bound in the presence of 5 µg ml⁻¹ unlabelled thrombin. □, Radioactivity in the 65K component and bound but unlinked ¹²⁵I-thrombin; ●, c.p.m. in the 65K component.

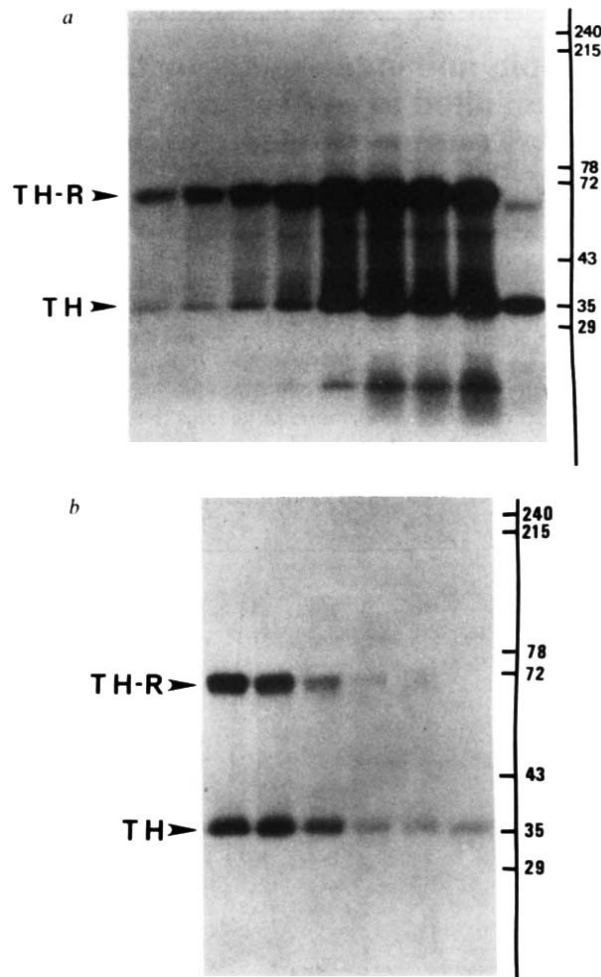


Fig. 4 Time courses of the formation and disappearance of Th-R. *(a)*, Using the procedures described in Fig. 3a, HF cells were incubated with ¹²⁵I-thrombin (50 ng ml⁻¹) for various periods at 37 °C, and prepared for SDS-PAGE as described in Fig. 1a. Samples were applied to slab gels containing 5–20% linear polyacrylamide gradients and 0.1% SDS, and autoradiographs were made. Lanes 1–8 show the results of 20 s, 40 s, 80 s, 160 s, 9 min, 30 min, 60 min and 90 min incubations, respectively. Lane 9 shows the result of a 30-min incubation with ¹²⁵I-thrombin when 8 µg ml⁻¹ unlabelled thrombin was present. *b*, Cultures incubated with 50 ng ml⁻¹ ¹²⁵I-thrombin for 90 min were quickly rinsed six times with 2 ml ice-cold PBS, and incubated for various periods at 37 °C with 3 ml DV HEPES medium containing 8 µg ml⁻¹ unlabelled thrombin. The cells were then rinsed twice with cold PBS and processed for SDS-PAGE as described in Fig. 1a. The samples were applied to slab gels containing 7.5–15% linear polyacrylamide gradients and 0.1% SDS, and an autoradiograph was prepared. Lanes 1–6 show the results of 0, 10, 30, 270 and 360 min incubations, respectively, following removal of ¹²⁵I-thrombin-containing medium. In lane 6 cultures were treated as in lane 4, except that the ¹²⁵I-thrombin incubation was carried out in the presence of 8 µg ml⁻¹ unlabelled thrombin.

1-h incubation with ¹²⁵I-EGF, most of the EGF-R was insensitive to trypsin, suggesting that it had entered the cells. During ¹²⁵I-EGF incubations longer than 1 h, iodinated components of approximate MWs 70,000, 50,000 and 36,000 appeared (Fig. 2a, lanes 3, 4). Figure 2b shows that these resulted from processing or degradation of EGF-R. When cultures incubated with ¹²⁵I-EGF were rinsed and incubated at 37 °C with medium containing no EGF, the unlinked ¹²⁵I-EGF disappeared from the cells within 1–2 h, but much of the EGF-R remained (Fig. 2b, lanes 1–3). During the next 2 h, most of the EGF-R was degraded to a component of MW 36,000, and additional products of 70,000 and 50,000 MWs (Fig. 2b, lanes 3, 4). Degradation of EGF-R occurred more rapidly if EGF was present in the medium. Similar results have been obtained in studies with mouse cells in which the fate of the EGF receptor covalently linked to ¹²⁵I-EGF through a photoactivated cross-linking reagent was studied^{9,10}.

These results with EGF prompted us to determine whether thrombin, another highly purified growth factor for HF cells¹⁴, also became linked to its receptors during mitogenic stimulation. Fibroblasts possess a large number of specific high-affinity thrombin receptors (about 2×10^5 receptors per cell with a K_d of 1×10^{-9} M in mouse cells)¹⁵. Binding to these receptors is apparently necessary for thrombin-stimulated cell division¹⁵. When HF cells were exposed to ^{125}I -thrombin ($0.25 \mu\text{g ml}^{-1}$) for 90 min at 37°C , most of the specifically bound radioactivity migrated with material larger than ^{125}I -thrombin, and about one-third of the specifically bound radioactivity was linked in a well defined complex of MW 65,000 (65 K component) (Fig. 3a). Because the MW of thrombin after reduction is about 30,000 (ref. 16), this indicated linkage to a receptor of about 35,000. (However, these MWs are only rough estimates, as thrombin is a glycoprotein.) The remainder of the specifically bound radioactivity migrated with free thrombin and heterogeneous material that was smaller than the 65K cross-linked complex but larger than thrombin. As with EGF-R, the ^{125}I -thrombin-receptor complex (Th-R) survived treatment with 3% SDS and 1% 2-mercaptoethanol in a boiling water bath for 5 min, suggesting that this linkage is also covalent. The Th-R probably resulted from interaction of ^{125}I -thrombin with cell receptors because it was absent either when ^{125}I -thrombin was incubated without cells (data not shown), or when a vast excess of unlabelled thrombin was added to inhibit interaction of ^{125}I -thrombin with its receptors (Fig. 3a).

Cellular formation of Th-R was apparent at a thrombin concentration of 2 ng ml^{-1} , and approached a maximum at $0.4 \mu\text{g ml}^{-1}$ ^{125}I -thrombin. The concentration dependence of Th-R formation and total specific ^{125}I -thrombin binding exhibited a similar concentration dependence (Fig. 3b). Interestingly, the dose dependence of thrombin for stimulation of HF cell DNA synthesis approximately corresponds to that for Th-R formation (unpublished results), consistent with the possibility that Th-R transmits the mitogenic signal.

Formation of Th-R by HF cells incubated with ^{125}I -thrombin at 37°C could be detected within 20 s, and reached steady-state within 30 min (Fig. 4a). In contrast, the amount of bound but unlinked ^{125}I -thrombin (Th) increased more slowly. The rapidity of Th-R formation suggested that this linkage occurred at the cell surface. This was confirmed by the finding that a 10-min treatment with trypsin ($10 \mu\text{g ml}^{-1}$) at 37°C removed Th-R formed after a 3-min incubation of cells with ^{125}I -thrombin. After a 90 min binding incubation most of the Th-R was insensitive to trypsin, suggesting that it had been internalised. We found no evidence of discrete degradation fragments from Th-R. When cultures incubated with ^{125}I -thrombin were rinsed and incubated at 37°C with medium containing unlabelled thrombin, Th-R gradually disappeared over 4 h without the appearance of other bands (Fig. 4b).

We have reported here a novel interaction of human cells with two protein mitogens, EGF and thrombin. Both molecules became linked to their specific cell surface receptors, both linkages seemed to be covalent, and in both cases the coupled growth factor-receptor complexes apparently entered the cells. These linkages were not caused merely by transfer of ^{125}I from the growth factors to receptors, as chymotryptic digestion of EGF-R and Th-R released polypeptide fragments of ^{125}I -EGF and ^{125}I -thrombin, respectively.

The finding that polypeptide factors become linked to cell surface receptors is unexpected but not inconsistent with current knowledge. The direct linkage of EGF to cell surface receptors of normal and transformed murine cells and isolated membranes has been found simultaneously by Linsley *et al.* and is reported in the accompanying paper¹⁷. Insulin and trypsin have also been reported to become tightly associated with cell components^{18,19}, although it is unclear from these reports whether these associations survive treatment with SDS. In studies on the interaction of ^{125}I -insulin with H-4 hepatoma cells, a significant quantity of what seems to be an insulin-receptor complex (MW 120–130,000) was found, and was resistant to treatment with

SDS and 2-mercaptoethanol (C. Hoffman and D. F. Steiner, personal communication). Direct linkage of polypeptide hormones and growth factors to cell surface receptors might be a general phenomenon which will facilitate both the identification of these receptors and study of their metabolic fate. The role of polypeptide-cell surface receptor complexes in the action of these polypeptides remains to be studied. However, Shechter *et al.* recently concluded that the growth stimulatory effects of EGF "may be mediated by occupation of only a negligible fraction of very high-affinity binding sites" (ref. 20). The present data are consistent with the possibility that this "very high-affinity" binding represents EGF-R.

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JOFFRE B. BAKER
ROBERT L. SIMMER
KEVIN C. GLENN
DENNIS D. CUNNINGHAM

Department of Microbiology,
College of Medicine,
University of California,
Irvine, California 92717

Received 27 November 1978; accepted 26 February 1979.

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Direct linkage of epidermal growth factor to its receptor

EPIDERMAL GROWTH FACTOR (EGF), a potent polypeptide mitogen, has been studied intensively by those concerned with the molecular events leading to cell proliferation^{1–4}. The initial, reversible interaction of EGF with a specific cell surface receptor and the subsequent internalisation and degradation of EGF, and by inference the EGF-receptor complex, are well documented, although the role of these events in mitogenesis is unknown^{4–6}. In an attempt to define this role, we used photoaffinity probes to specifically cross-link radiolabelled EGF to its receptor, a 185,000-dalton polypeptide on the surface of murine 3T3 cells⁷. These probes also enabled us to follow the metabolic fate of this receptor⁸. We have since noted that a small portion of the underivatised radiolabelled EGF that binds specifically to 3T3 cells or isolated 3T3 cell membranes becomes directly and irreversibly linked to a polypeptide of molecular weight (MW) 185,000. Here, we document this association and

show that the resulting complex has properties identical to those of the EGF-receptor complex originally identified by photoaffinity labelling.

When 3T3 cells were incubated with ^{125}I -EGF, and the proteins solubilised in ionic detergent solution and subjected to electrophoresis, 1–2% of the specifically bound label migrated as a band of apparent MW 190,000 (Fig. 1, lane A). The radioactivity in this band was reduced when unlabelled EGF was included with labelled EGF in the binding medium (Fig. 1, lanes C, E), an indication that the appearance of the 190,000 MW band requires specific binding of EGF.

EGF resembles certain other hormones in its capacity to reduce the number of available specific receptor sites when incubated with cultured cells^{3–6,8}. This ligand-induced reduction of binding activity is termed 'down regulation', and in the case of the EGF receptor, occurs by internalisation of the receptor protein⁸. When 3T3 cells were treated with unlabelled EGF to down-regulate the EGF receptor before addition of labelled EGF, formation of the direct linkage complex was greatly reduced (Fig. 1, lane G), a further indication that complex formation requires EGF specific binding. Also, when cells were incubated with labelled EGF for longer periods, radioactivity disappeared from the 190,000 MW direct linkage complex and appeared in the same three degradation products that are formed during down-regulation of the photoaffinity-labelled EGF-receptor complex (Fig. 1, lanes B, D, F)⁸. These data show that a small amount of the ^{125}I -radioactivity in specifically bound EGF becomes directly linked with its receptor.

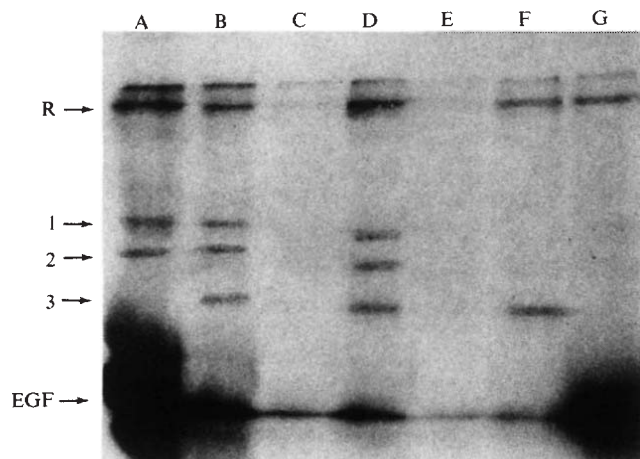


Fig. 1 Formation of the direct linkage complex and the derived metabolic products during down-regulation. Monolayer cultures of Swiss mouse 3T3 cells (clone 42) were grown on plastic dishes, as previously described⁷. Confluent cultures were washed three times with binding medium (DMEM, without NaHCO_3 but containing 10 mM HEPES and 1.0 mg ml^{-1} bovine serum albumin). Some samples were incubated with 50 ng ml^{-1} unlabelled EGF for 4 h at 37°C to allow for down regulation of receptor. All samples were incubated for 30 min at 37°C with iodinated EGF⁷, at 50 ng ml^{-1} (1.5×10^5 c.p.m. per ng) in binding medium, and excess unlabelled EGF was added where noted. The ^{125}I -EGF preparations used contained 0.5–1.0 atoms of iodine per mol of EGF. The cells were washed to remove unbound labelled EGF, then incubated in binding medium at 37°C for the indicated times, washed again, frozen, thawed and dissolved in electrophoresis sample buffer (ESB: 63 mM Tris, pH 6.8, 3% SDS and 10% glycerol). Aliquots of 100 μl of each sample were subjected to electrophoresis on a 10% acrylamide gel, using the discontinuous system of Laemmli¹¹. On completion of electrophoresis, the slabs were stained with Coomassie blue, destained, dried on filter paper, and autoradiographed on X-ray film (Kodak no screen NS-2T). The band of radioactively labelled material visible at the interface between the stacking and resolving gels in this experiment is not present when samples are boiled or subjected to shear forces before electrophoresis, conditions which do not quantitatively alter the amount of radioactivity present in the receptor band. (A) Formation of the direct linkage complex (R) by incubation of cells with ^{125}I -EGF for 30 min at 37°C. (B) Formation of receptor degradation products (I, II and III) when samples from (A) were incubated in binding medium for an additional 30 min at 37°C. (C) As (B), but with 500 ng ml^{-1} of unlabelled EGF present during ^{125}I -EGF binding. (D) as (B), but with 60 rather than 30 min of additional incubation. (E) as (D), but with 500 ng ml^{-1} unlabelled EGF present during ^{125}I -EGF binding. (F) As (B), but with 120 rather than 30 min of additional incubation. (G) Cells were incubated with 50 ng ml^{-1} of unlabelled EGF for 4 h at 37°C to down regulate the EGF receptor before ^{125}I -EGF binding.

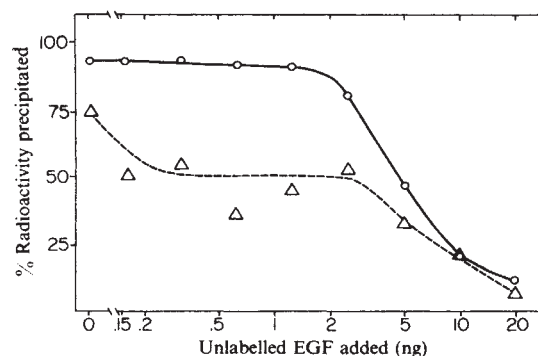


Fig. 2 Immune precipitation of specifically bound EGF and the EGF-receptor direct linkage complex. ^{125}I -EGF was bound to cells for 60 min at 23°C as described in Fig. 1. After washing to remove unbound EGF, the cells from three 78-cm² dishes were scraped into binding medium and sedimented in a Brinkman microfuge. The cells were vigorously mixed for 2 min with 0.9 ml of 0.5% (v/v) Triton X-100 in binding medium and then incubated for an additional 10 min at 23°C. Insoluble material was removed by sedimentation for 2 min in a microfuge; more than 90% of the cell-bound radioactivity and the bulk of the direct linkage complex remained in the supernatant fraction. Determination of immune precipitable total cell-bound EGF (O): 100 μl of the supernatant fraction were mixed with 10 μl of binding medium containing the indicated amounts of unlabelled EGF. To this, 10 μl of binding medium containing 1 μg of IgG fraction¹² of rabbit anti-EGF¹³ were added and the samples incubated for 30 min at 4°C, after which, 10 μl of 10% (v/v) solution of formalin-fixed *Staphylococcus aureus*, an immune adsorbent¹⁴, were added. After a 15-min incubation at 4°C, the immune adsorbent was sedimented for 2 min in a microfuge and the radioactivity present in the pellet and supernatant fractions measured to determine the per cent of total radioactivity which adhered to the immunoadsorbent. Determination of immune precipitable EGF-receptor direct linkage complex (Δ). Each pellet and supernatant fraction from the immunoadsorption experiment was treated to achieve the stated concentrations of the components in ESB, boiled and centrifuged to remove the immune adsorbent. Samples were subject to electrophoresis on a 10% acrylamide slab¹¹, and the region of the gel containing the direct linkage complex excised for measurement of radioactivity.

As direct linkage could result from transfer of labelled iodine from ^{125}I -EGF to its receptor, we used an antiserum specific for EGF to determine the immunoreactivity of the labelled 190,000 MW protein in non-ionic detergent extracts (Fig. 2). The bulk of the radioactivity initially present in both total cell-associated EGF and in the direct linkage complex was immune precipitated by antiserum to EGF. Also, unlabelled EGF similarly inhibited the precipitation of both the direct linkage complex and total cell-associated EGF. This last observation shows that much of the direct linkage complex consists of a single immunoreactive EGF molecule in stable association

Table 1 Time course of ^{125}I -EGF binding and direct linkage complex formation with a cell surface membrane preparation

	Incubation temperature (°C)	Incubation time (h)	
		1	2
Total binding (c.p.m.)	0	1,658	1,546
	23	3,547	2,777
	37	3,602	2,686
Direct linkage complex (c.p.m.)	0	10	49
	23	21	112
	37	43	120

3T3 cells were grown to confluence on 3,400 cm² of surface area in Dulbecco's modified Eagle's medium (DMEM) + 10% fetal calf serum (FCS) for preparation of cell surface membranes¹⁶. Particulate fractions banding at less than 40% (w:w) sucrose were pooled and collected by sedimentation. The membranes were suspended in binding medium and divided into three aliquots of 1.0 ml; 0.11 ml of ^{125}I -EGF (2.1×10^5 c.p.m. per ng, 500 ng ml^{-1}) in binding medium was added to each tube for incubation at 0, 23 or 37°C. Incubations were terminated by layering a 0.1-ml aliquot from each tube above a 1 ml cushion of 10% (w:w) sucrose in binding medium and sedimenting for 2 min in a Brinkman microfuge. The pellets were washed with 1.5 ml binding medium. Total binding was corrected for background binding measured at zero time and was approximately 90% specific. The radioactivity in direct linkage complex was measured as described in Fig. 1 and was also corrected for background binding.

with its high MW receptor protein. However, this does not eliminate the possibility that the direct linkage complex forms through attachment of receptor to an artefactual and highly reactive EGF species produced during radioiodination. We therefore repeated the experiment described in Fig. 2 using unlabelled EGF and cells labelled metabolically with ^{35}S -methionine. Using these cells we identified a high MW ^{35}S -labelled protein band with electrophoretic mobility identical to that of the ^{125}I -EGF receptor direct linkage complex and which was only formed in cells incubated with EGF (data not shown).

Two independent experiments show that the photoaffinity-labelled EGF-receptor complex is degraded in the lysosomes⁸: the degradation products co-fractionate with lysosomal enzyme markers during organelle fractionation, and the degradation of the photoaffinity complex is inhibited by the lysosomotropic drug, chloroquine⁹. The degradation of the direct linkage complex is also markedly inhibited by chloroquine (Fig. 3a), and the rates of degradation (Fig. 3b) in the presence and absence of chloroquine are similar to those previously determined for the photoaffinity-labelled complex⁸.

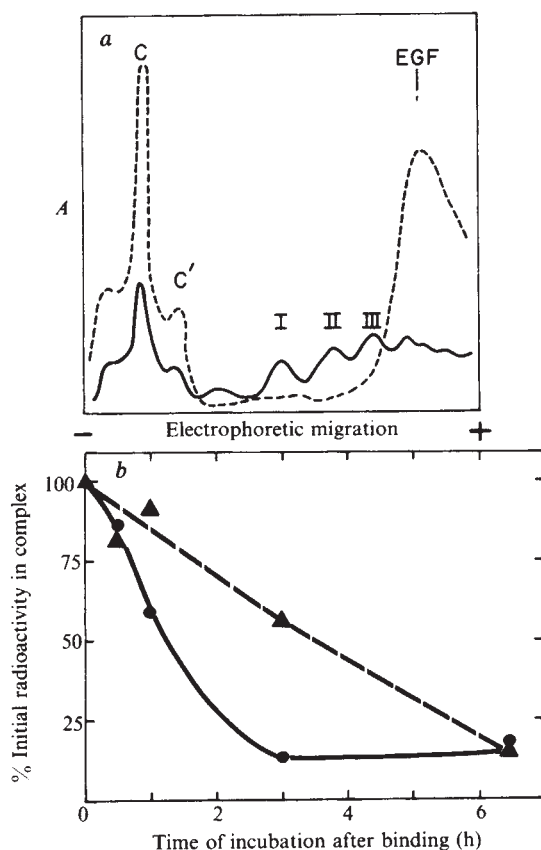


Fig. 3 a, Degradation of the direct linkage complex and inhibition of degradation by chloroquine. The conditions are essentially those described in Figs 1 and 2. Binding was for 1 h at 23 °C; following binding, and before preparation for electrophoresis, the cultures were incubated at 37 °C for an additional 75 min. The X-ray films were scanned with a densitometer, and the tracings are reproduced. —, Degradation of the direct linkage complex (C) into the proteolysis products characteristic of the EGF-receptor cross-linked complex. C' is a high MW product (142,000) that accumulates in the presence of chloroquine⁸. Bands I, II and III have apparent MWs of 59,000, 38,000 and 30,000 in this particular gel system. - - - -, Inhibition of direct linkage complex processing by chloroquine. Conditions were as described for Figs 1 and 2. Chloroquine (0.1 mM) was added 15 min before EGF and was present throughout the experiment. b, Effects of prior treatment with chloroquine on the rate of degradation of the direct linkage complex. Conditions were the same as in a, except that chloroquine was added 1 h before EGF. At the indicated times, samples were prepared for electrophoresis, which was carried out on a 10% acrylamide slab. The direct linkage complex was located on the dried gel by autoradiography. The amount of radioactivity present as direct linkage complex at an indicated time of incubation is expressed as a % of the amount of complex present before incubation. ●, No chloroquine added; ▲, plus 0.1 mM chloroquine.

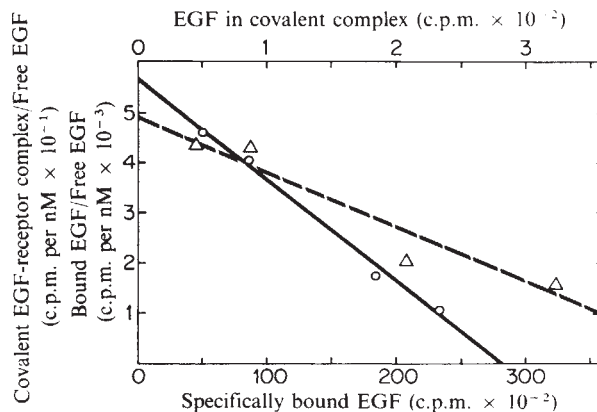


Fig. 4 Correlation between the concentration dependence of EGF binding and direct-addition complex formation. Cells grown as described in Fig. 1 were incubated for an additional day in DMEM plus 0.8% FCS. The cells were washed with binding medium, and total binding was determined at 23 °C after a 65-min incubation with iodinated EGF (2.3×10^5 c.p.m. per ng) at 3.75, 7.5, 37.5 and 75 ng ml⁻¹. Nonspecific binding was measured on duplicate cultures in the presence of $1 \mu\text{g ml}^{-1}$ unlabelled EGF. Cultures were washed to remove unbound EGF and the samples were solubilised with 0.1 ml ESB and quantitatively transferred for determination of cell-bound radioactivity. Specifically bound EGF (○) was calculated by subtracting nonspecifically bound EGF from the total amount bound. The resulting binding data were plotted according to Scatchard¹⁵; the slope of the curve is thus proportional to the K_A of binding. The samples were then processed for electrophoresis as in Fig. 1. The regions containing the direct linkage complex were excised from the dried gel and total radioactivity was corrected for the nonspecific radioactivity remaining when $1 \mu\text{g ml}^{-1}$ unlabelled EGF was present. The specific radioactivity in the complex at a particular EGF concentration was calculated as the fraction of the total radioactivity applied at that concentration (△). Each point is the average of two determinations, except for the point at 75 ng ml⁻¹ EGF, which is the average of four determinations. For broken line, $-\text{slope} = K_{\text{formation}} = 0.112 \text{ nm}^{-1}$; for solid line, $-\text{slope} = K_A = 0.201 \text{ nm}^{-1}$.

If the direct linkage EGF-receptor complex is a complex of EGF and its physiological receptor, the saturability for reversible EGF binding and direct complex formation should be similar. The observed concentration dependence for complex formation, $K_{\text{formation}}$, closely approximated the equilibrium binding constant, K_A , for EGF and its physiological receptor in the intact cell (Fig. 4 and data not shown). Table 1, which shows that complex formation is a slower process than binding, may partly explain the slight discrepancy between $K_{\text{formation}}$ and K_A . This should be accentuated at lower EGF concentrations, where longer periods of time are required to achieve binding equilibrium. Accordingly, the apparent $K_{\text{formation}}$ is an underestimate of its true value. Table 1 also shows that complex formation is more sensitive to a temperature decrease than is binding, and indicates why direct linkage of EGF to its receptor was not observed in our earlier studies with ^{125}I -EGF photoaffinity probes^{7,8}. A comparison of the times and temperatures of exposure to EGF to receptor for direct labelling (Table 1) with those used in the photoaffinity labelling studies^{7,8} shows that direct complex formation would account for less than 10% of the cross-linked complex formed on photolysis^{7,8}.

Thus, we have demonstrated that a small fraction of the EGF specifically bound to its cell surface receptor becomes strongly and directly linked to a high MW protein. This complex and the photoaffinity-labelled EGF-receptor complex have the same biological fate. The biological and chemical properties of the complex, described above are those expected of a covalently linked EGF-receptor complex.

We are now investigating the chemical nature and mechanisms of formation of the complex. Its members are not joined by a disulphide bond—it is not dissociated by boiling in 5% 2-mercaptoethanol. Its formation does not seem to be catalysed by a transglutaminase reaction similar to that responsible for intermolecular protein cross-linking in the red blood cell¹⁰—complex formation is not increased by Ca^{2+} ion, or decreased by added amines such as histamine, glycine ethyl ester or cystamine. Alkylation of the amino terminus of EGF with

biotin¹⁷ did not affect EGF binding, but substantially inhibited direct complex formation, implicating a site on or near the amino terminus of EGF in direct complex formation.

We also have evidence for an EGF-receptor complex in SV40-transformed 3T3 cells, normal human fibroblasts and a human tumour cell line (A-431)^{5,18}; it is also formed when EGF is incubated with human placental membranes. Baker *et al.* (see accompanying paper) have independently detected a EGF-receptor complex in cultured human fibroblasts and have evidence of complex formation between thrombin and its receptor in human foreskin fibroblasts¹⁹. Recently, a complex of insulin and a protein of MW approximately 120,000–130,000 was detected in cultured H-4 cells incubated with ¹²⁵I-insulin; this complex resists dissociation in SDS and accounts for at least 10% of the insulin which binds specifically to these cells (C. Hoffman and D. Steiner, personal communication). A high MW form of ¹²⁵I-insulin, accounting for at least 10% of the radioactivity specifically bound to adipocytes, was detected by Kahn and Baird²⁰; this passes through Sephadex G-50 at the void volume in aqueous solution containing 0.1% Triton X-100, 4 M urea and 1 M acetic acid. We have incubated 1 nM ¹²⁵I-insulin with cultured L1-3T3 cells either before or after they differentiated to form adipocytes²¹ and find a substantial quantity of a component of MW 125,000 ± 5,000 which resists dissociation to form free insulin during 5 min of boiling in aqueous 3% SDS (Iwata, K. and C.F.F., unpublished observation). Taken together, these observations indicate that the direct linkage phenomenon may be a general one, a correlation between the high affinity specific binding of many polypeptide ligands and their cell surface receptors.

Although a biological role for direct linkage of hormones to their specific receptors has not been shown, Schechter *et al.* have concluded that a small fraction of "very high affinity binding sites"—possibly identical to the direct complex—may play a role disproportionate to their fraction of the whole in mediating EGF action²².

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PETER S. LINSLEY
CINDY BLIFELD
MICHAEL WRANN
C. FRED FOX

Molecular Biology Institute,
University of California at Los Angeles,
Los Angeles, California 90024

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Is stimulation of benzodiazepine receptor binding mediated by a novel GABA receptor?

A STEREOSPECIFIC, saturable, high affinity binding site for ³H-diazepam has recently been characterised in membrane fractions isolated from the brains of mammals¹, including man², which has been suggested to represent the pharmacological benzodiazepine (BZ) receptor^{2–4}. Electrophysiological⁵ and biochemical⁶ results indicate that BZs exert their main actions in the central nervous system by facilitation of the synaptic action of γ -aminobutyric acid (GABA). Evidence for an interaction between GABA and BZs at the receptor level has recently been obtained^{7–11}. Thus, GABA has been shown to stimulate BZ binding^{8–11} and there is preliminary evidence that this process is mediated by a specific GABA recognition site, as the GABA agonists muscimol⁸, imidazoleacetic acid¹¹, and 3-guanidino-propionic acid¹¹ also stimulate ³H-diazepam binding. We now report different structural requirements for stimulation of ³H-diazepam binding to rat brain synaptic membranes compared with those for inhibition of Na⁺-independent ³H-GABA binding¹². We suggest that stimulation by GABA of BZ receptor binding involves a novel type of a GABA receptor.

Specific BZ receptor binding was determined with previously frozen and extensively washed membrane fractions from rat brain cerebral cortex with 1 nM ³H-diazepam as labelled ligand¹¹. Specific binding of 5.8 nM ³H-GABA to Triton X-100-treated membranes⁷ was measured using a centrifugation assay¹³.

The structural analogues of GABA in Fig. 1 were examined as stimulators of ³H-diazepam binding. In general, the concentrations of GABA analogues required for 50% activation of ³H-diazepam binding (EC₅₀) were higher than those required for 50% inhibition of Na⁺-independent ³H-GABA binding (IC₅₀). A comparison of the ratios EC₅₀:IC₅₀ revealed remarkable differences. Dihydromuscimol, GABA, and 4-amino-3-hydroxybutyric acid, relatively flexible molecules which can adopt a variety of conformations, exhibited the lowest ratios. Muscimol, thiomuscimol, and *trans*-4-aminocrotonic acid, although still flexible molecules but compounds with partially flattened structures, displayed relatively higher affinities for Na⁺-independent ³H-GABA binding sites. Compounds with even more rigid and flattened structures such as isoguvacine and 4,5,6,7-tetrahydroisoxazolo(4,5-c)pyridin-3-ol (THIP) had very little effect on ³H-diazepam binding but were potent inhibitors of Na⁺-independent ³H-GABA binding. On the other hand, isoguvacine and THIP did not display properties of (partial) antagonists as they failed to modify the submaximal stimulation of ³H-diazepam binding induced by 3 μ M GABA or by 1 μ M muscimol (data not shown). These results point to the existence of a distinct GABA recognition site associated with the BZ receptor, as the structural requirements for the activation of BZ receptor binding are different from those for inhibition of Na⁺-independent ³H-GABA binding.

On extending some previous work^{8,9,11} we found that the effects of all GABA analogues which stimulated ³H-diazepam binding could be antagonised by low concentrations of ($\pm$)-bicuculline-methiodide (10 μ M). In contrast, picrotoxin (30 μ M) had no significant effects on basal or GABA-stimulated ³H-diazepam binding.

The proposed new GABA recognition site is different from the GABA high affinity uptake site as well as the Na⁺-independent ³H-GABA binding site, as potent GABA uptake inhibitors such as guvacine, β -alanine and nipecotic acid^{14,15} had no effect on ³H-diazepam binding. In contrast to Na⁺-dependent ³H-GABA binding, stimulation of ³H-diazepam binding was antagonised by bicuculline-methiodide, enhanced by freezing and thawing¹¹ and insensitive to pretreatment of the membranes with phospholipase A⁹.

Compound	Formula	Activation of ³ H-Diazepam binding EC ₅₀ (μM)	Inhibition of ³ H-GABA binding IC ₅₀ (μM)	EC ₅₀ IC ₅₀
(RS)-4,5-Dihydro-muscimol		0.22	0.041	5.4
Muscimol		0.35	0.015	23
GABA		1.15	0.14	8.2
trans-4-Amino-crotonic acid		1.15	0.060	19
Thiomuscimol		1.50	0.15	10
(RS)-4-Amino-3-hydroxy-butyric acid		17.8	2.60	6.9
3-Guanidino-propionic acid		71.0	3.60	20
Imidazole-acetic acid		89.0	1.20	74
Homomuscimol		290	8.0	36
Isoguvacine		> 300	0.45	> 500
THIP		> 300	0.80	> 500
Guvacine		> 300	> 100	—
(RS)-Nipeccotic acid		> 300	> 100	—
Gabaculine		> 300	> 100	—

In conclusion, stimulation of ³H-diazepam binding seems to be the result of a specific interaction of GABA-like drugs with a novel type or different functional state of a GABA receptor. The distinct structural requirements for stimulation of BZ receptor binding might allow the development of new GABA agonists with selective therapeutic actions.

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MANFRED KAROBATH*
PETER PLACHETA†
MARGIT LIPPITSCH

Department of Biochemical Psychiatry,
Psychiatrische Universitätsklinik Wien,
Vienna, Austria

POVL KROGSGAARD LARSEN

Department of Chemistry BC,
Royal Danish School of Pharmacy,
Copenhagen, Denmark

Received 12 January; accepted 5 March 1979.

*To whom correspondence should be addressed at: Psychiatrische Universitätsklinik, Lazarettgasse 14, A-1090 Wien, Austria.

†Permanent address: Institute of Pharmacology, University of Vienna, Vienna, Austria.

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Fig. 1 Stimulation of ³H-diazepam binding and inhibition of Na⁺-independent ³H-GABA binding by GABA analogues. Crude synaptic membranes isolated from rat cerebral cortex were frozen at –20 °C for at least 18 h and then washed 5 times by rehomogenisation in 40 vol 50 mM Tris-HCl buffer (pH 7.4)¹¹. Specific ³H-diazepam binding was determined in triplicates as previously described¹¹. The incubation medium contained membranes (about 250 μg of protein), 1.0 nM ³H-diazepam in 100 mM Tris-HCl buffer pH 7.4 plus compounds to be tested. At the end of the incubation period (0 °C, 90 min) 5 ml ice-cold buffer (50 mM Tris-HCl, pH 7.4) was added immediately and membranes with bound ³H-diazepam were trapped on Whatman GF/B glassfibre filters. The filters were instantly washed with additional 5 ml ice cold buffer and specific binding was determined after subtraction of unspecific binding in the presence of excess (3 μM) unlabelled diazepam. In the presence of a saturating concentration of GABA (30 μM) ³H-diazepam binding was stimulated between 81 and 128% over basal binding. The test compounds were used in at least four concentrations. The following compounds structurally related to GABA (not listed in Table 1) were examined at 100 μM concentration and found to be inactive (less than 10% stimulation) in stimulating specific ³H-diazepam binding: glycine, taurine, glutamic acid, homocarnosine, baclofen, aminooxyacetic acid, γ-vinyl GABA, γ-acetylenic GABA, δ-amino-levalulinic acid; 5-amino-valerianic acid and β-alanine were weak activators with EC₅₀ values >100 μM. For the determination of specific ³H-GABA binding crude synaptic membranes from rat cerebral cortex were frozen at –20 °C for at least 24 h and treated for 30 min at 37 °C with 0.01% Triton X-100⁷. After centrifugation at 40,000g for 15 min the pellet was dispersed with an Ultra-Turrax in 50 vol 50 mM Tris-citrate buffer (pH 7.1) without Triton X-100. This centrifugation was repeated twice. For specific ³H-GABA binding¹³ aliquots of membranes were incubated in quadruplicate at 4 °C for 5 min in 0.5 ml 50 mM Tris citrate buffer (pH 7.1) containing 5.8 nM ³H-GABA, alone, or in the presence of 4 mM GABA, or in the presence of at least four concentrations of compounds to be tested. After incubation, the reaction was terminated by centrifugation for 10 min at 40,000g. The supernatant was discarded, the pellet rapidly rinsed with cold H₂O and dissolved in NCS (Amersham) solubiliser before counting. The s.e.m.s of ³H-GABA or ³H-diazepam binding measurements at a single drug concentration were less than 4%. IC₅₀ and EC₅₀ values were determined from log-probit concentration curves and were reproducible within ±15% of the values given (Means of 2–4 separate determinations).

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Regulation of muscle acetylcholine receptor synthesis *in vitro* by cyclic nucleotide derivatives

STRONG evidence indicates that muscle activity represses the synthesis of extra-synaptic acetylcholine receptor (AChR) in vertebrate skeletal muscle—(1) electrical stimulation of adult denervated muscle prevents the development of acetylcholine supersensitivity^{1,2} and blocks the incorporation of radiolabelled amino acids into the AChR protein³; (2) *in vitro*, electrical stimulation of embryonic myotubes also causes a decrease in the rate of AChR synthesis; moreover, the abolition of the spontaneous contraction of the myotubes by tetrodotoxin (TTX)

leads to an increase of newly synthesised receptor molecules⁴⁻⁶; (3) chronic paralysis of the neuromuscular junction by cholinergic antagonists increases the synthesis of extrasynaptic AChR in adult and embryonic myofibre⁷⁻⁹. In addition, it has been claimed that 'trophic' factors other than the neurotransmitter acetylcholine¹⁰⁻¹⁴ regulate the level of extrasynaptic AChR. We show here that the synthesis of AChR in cultured embryonic myotubes is modified by cyclic nucleotide derivatives, and we suggest that cyclic nucleotides may serve as intracellular signals¹⁵ in both activity-mediated and neurotrophic control of extrasynaptic AChR synthesis.

Myoblasts were obtained from the hind limbs of 11-d-old chick embryos by mechanical dissociation¹⁶, seeded in gelatin-coated plastic dishes and cultivated in a 3:1 mixture of Dulbecco's modified Eagle's medium and medium 199 (Gibco) containing 10% horse serum (Gibco) and 1% chick embryo extract¹⁷. From 48 to 96 h of culture, the cells were treated with 10^{-5} M cytosine arabinoside to minimise fibroblast proliferation¹⁸. After the second day, the media were changed daily. For the quantitation of cell surface AChR sites, the myotubes were labelled with 10 nM 125 I- α -bungarotoxin for 1 h at 37°C, washed three times with phosphate-buffered saline, solubilised in 1 M NaOH containing 1% Triton X-100, and the 125 I-radioactivity bound per culture dish was determined in a γ -counter. All toxin binding data were corrected for nonspecific binding determined in the presence of 10^{-5} M decamethonium (always below 3% of total binding).

Addition of the membrane depolarising agent veratridine¹⁹ to myotubes from 7-d-old cultures significantly decreased the

number of α -bungarotoxin binding sites per culture dish to below control levels (Fig. 1). In the same conditions, and in agreement with other authors^{4,6}, blocking of the myotube electrical activity by TTX increased α -toxin binding. Up to the third or fourth day in culture, veratridine and TTX (data not shown) had little effect on AChR accumulation; presumably, at that stage the cells have not developed action potential sodium channels sensitive to these compounds.

In 2- and 7-d-old cultures, dibutyryl cyclic GMP decreased, whereas dibutyryl cyclic AMP and prostaglandin E_1 (PGE₁) increased the number of α -bungarotoxin binding sites per culture dish (Fig. 1). On the other hand, 4×10^{-4} M butyrate had little if any effect on AChR expression (Table 1). Thus, the effect of dibutyryl cyclic nucleotides is nucleotide specific.

Figure 2 shows the concentration dependence of the inhibiting action of dibutyryl cyclic GMP on AChR accumulation; half-maximal inhibition occurred at $\sim 7 \times 10^{-5}$ M dibutyryl cyclic GMP. On the other hand, the half-maximal increase in α -toxin binding sites caused by dibutyryl cyclic AMP required concentrations of $1.3\text{--}1.5 \times 10^{-4}$ M (data not shown).

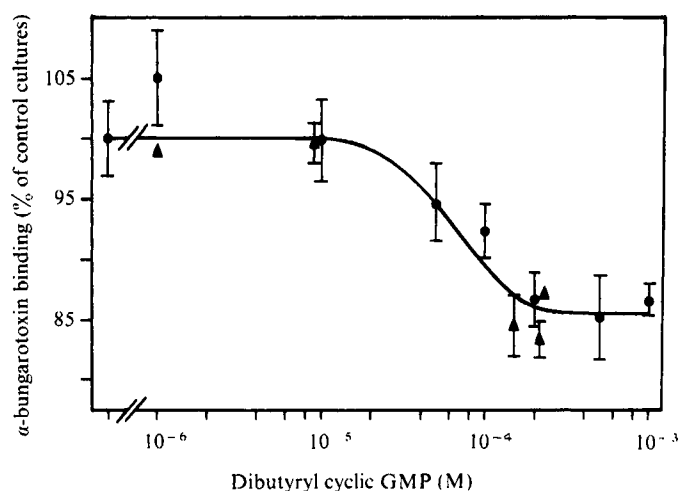


Fig. 2 Effect of increasing concentrations of dibutyryl cyclic GMP on the number of α -bungarotoxin binding sites in 4-d-old muscle cell cultures. Muscle cultures prepared as in Fig. 1 were treated with the indicated concentrations of dibutyryl cyclic GMP from 48 to 96 h of culture. ● and ▲, data from different independent experiments. The bars correspond to ± 1 s.e.m. ($n = 3\text{--}4$).

Two alternative mechanisms may explain the effect of dibutyryl cyclic nucleotides on AChR levels: a change in the rate of AChR synthesis, or a regulation of its rate of degradation. Because of the great stability of the α -bungarotoxin-AChR complex, the degradation of AChR can be followed after pulse-labelling of the myotubes with 125 I- α -bungarotoxin, the loss of bound 125 I-radioactivity being a measure of intracellular degradation of the AChR protein^{20,21}. Figure 3 shows that dibutyryl cyclic AMP or dibutyryl cyclic GMP do not significantly alter the rate of AChR degradation in cultured muscle cells. Therefore, these cyclic nucleotide derivatives regulate the synthesis of AChR or its insertion into the cytoplasmic membrane.

In another series of experiments, pre-existing AChR sites were blocked with unlabelled α -bungarotoxin and the appearance of new AChR monitored by 125 I- α -bungarotoxin binding. When these experiments were carried out using young myotubes (between 2 and 3 d *in vitro*) cultures treated with dibutyryl cyclic GMP bound less and those treated by dibutyryl cyclic AMP or PGE₁ bound more 125 I- α -bungarotoxin than the untreated controls (Table 1a). As expected, veratridine had no significant effect. Seven-day-old myotubes produced similar

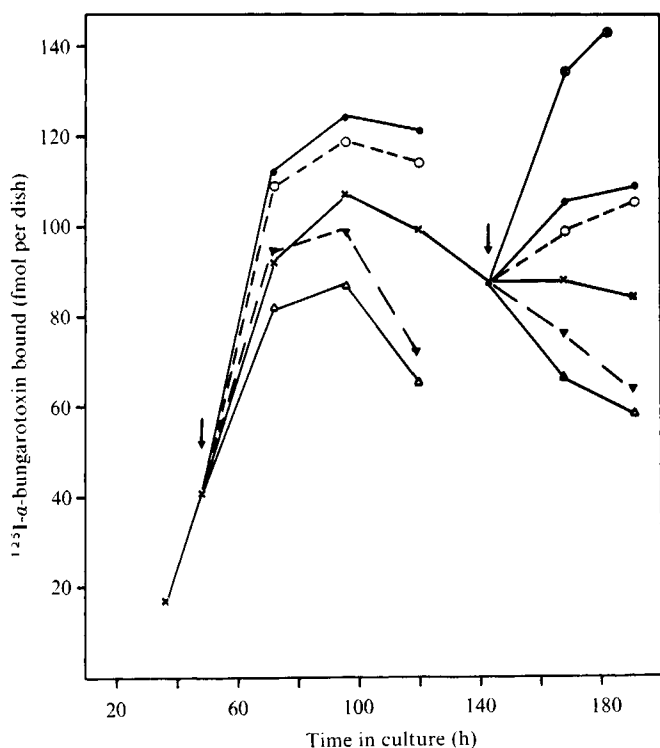


Fig. 1 Effects of veratridine, TTX, dibutyryl cyclic nucleotides and PGE₁ on the evolution of 125 I- α -bungarotoxin binding sites in muscle cultures. Myotubes were seeded at a density of 6×10^5 cells in a large number of 35-mm culture dishes. After 2 and 7 d in culture, the different reagents were added to several independent dishes. At the concentrations used, none of the additions had significant effects on the morphological differentiation of the cells. Culture condition: x, control; ▼, 1.5×10^{-6} M veratridine; ⊗, 10^{-6} M TTX; △, 2×10^{-4} M dibutyryl cyclic GMP; ●, 2×10^{-4} M dibutyryl cyclic AMP; ○, 10^{-5} M PGE₁. Each point represents the mean of at least two to three culture dishes.

Table 1 Accumulation of ^{125}I - α -bungarotoxin binding sites after saturation of pre-existing AChR sites with unlabelled α -bungarotoxin

Culture condition	Concentration (M)	^{125}I - α -bungarotoxin bound (c.p.m. $\pm$ s.e.m. per dish)	<i>n</i>
<i>a</i> , 2-d-old muscle cultures			
Control	—	44,778 $\pm$ 3,420	8
Veratridine	1.5×10^{-6}	41,062 $\pm$ 1,396	5
Dibutyryl cyclic GMP	2×10^{-4}	32,413 $\pm$ 2,486	5
Dibutyryl cyclic AMP	2×10^{-4}	56,676 $\pm$ 4,848	5
PGE ₁	10^{-5}	59,333 $\pm$ 591	3
Butyrate	4×10^{-4}	46,536 $\pm$ 4,100	3
<i>b</i> , 7-d-old muscle cultures			
Control	—	15,023 $\pm$ 1,412	7
Veratridine	1.5×10^{-6}	8,688 $\pm$ 1,318	4
TTX	10^{-6}	25,799 $\pm$ 1,624	6
Dibutyryl cyclic GMP	2.5×10^{-4}	7,772 $\pm$ 339	4
Dibutyryl cyclic AMP	2.5×10^{-4}	18,868 $\pm$ 568	4
TTX + veratridine	$10^{-6} + 1.5 \times 10^{-6}$	21,469 $\pm$ 2,466	5
TTX + dibutyryl cyclic GMP	$10^{-6} + 2.5 \times 10^{-4}$	8,473 $\pm$ 393	5
TTX + dibutyryl cyclic AMP	$10^{-6} + 2.5 \times 10^{-4}$	33,260 $\pm$ 1,676	4
Veratridine + dibutyryl cyclic GMP	$1.5 \times 10^{-6} + 2.5 \times 10^{-4}$	8,001 $\pm$ 588	5
Veratridine + dibutyryl cyclic AMP	$1.5 \times 10^{-6} + 2.5 \times 10^{-4}$	11,155 $\pm$ 847	4
Butyrate	4×10^{-4}	15,978 $\pm$ 1,810	3

A large set of identical embryonic chick muscle cultures was prepared by seeding 6.8×10^5 cells per 35-mm culture dish. After 40 h in culture, α -bungarotoxin was added to one-third of the dishes at a final concentration of $0.2 \mu\text{g ml}^{-1}$, and the cells were incubated at 37°C for 8 h. The medium was then removed, and the cells washed free of unbound α -bungarotoxin. After the addition of fresh medium and the indicated reagents, the cells were cultivated for a further 24 h before the determination of ^{125}I - α -bungarotoxin binding. The remaining cultures were grown for 7 d and then subjected to the same experimental protocol as described above for the 2 d-old cells. *n*, Number of culture dishes.

results, except that veratridine became almost as potent as dibutyryl cyclic GMP in reducing the appearance of new surface α -bungarotoxin sites (Table 1*b*). Furthermore, in these spontaneously contracting cells the TTX-induced increase in the appearance of α -bungarotoxin sites was completely abolished by dibutyryl cyclic GMP and partially antagonised by veratridine; in contrast, the combination of veratridine and dibutyryl

cyclic GMP did not lower the number of α -bungarotoxin binding sites below the value observed with dibutyryl cyclic GMP alone. These observations suggest that membrane depolarisation by veratridine and dibutyryl cyclic GMP regulates AChR synthesis through a common intracellular mechanism. On the other hand, the effect of dibutyryl cyclic AMP superimposes on those obtained with both TTX and veratridine, and so probably involves a different regulatory pathway.

Further evidence for different mechanisms of action for dibutyryl cyclic GMP and dibutyryl cyclic AMP comes from measurements of total protein synthesis (Table 2). Veratridine, TTX and dibutyryl cyclic GMP did not significantly modify the incorporation of ^{35}S -methionine into total myotube protein, but dibutyryl cyclic AMP increased the latter by about 30% over control. Thus, the increase of AChR synthesis by this cyclic AMP analogue might be due to a general enhancement of protein synthesis, whereas its blocking by dibutyryl cyclic GMP seems restricted to this particular (or to a few) protein(s).

Our experiments therefore demonstrate that in cultured myotubes, dibutyryl cyclic GMP (1) represses AChR synthesis in a similar fashion to the depolarising drug veratridine, and (2) abolishes the development of 'acetylcholine supersensitivity' induced by TTX. Cyclic GMP therefore seems to be a suitable candidate for the intracellular messenger of the activity-mediated control of extrasynaptic AChR synthesis. Recent experiments by Beam *et al.*²² with invertebrate and vertebrate nerve-muscle preparations have shown that both nerve and direct electrical stimulation raise the content of cyclic GMP in the adult muscle. In invertebrates, the latter process is Ca^{2+} -dependent²². Interestingly, in chick myotubes D-600, a blocker of Ca^{2+} -channels, stimulates AChR synthesis²³. Moreover, experiments carried out with myotubes from a dystrophic strain of mouse indicate that mechanical contraction is not required for the regulation of AChR synthesis²⁴. It is therefore tempting to speculate that the regulation of AChR synthesis by muscle electrical activity involves successively: (1) the opening of TTX- or veratridine-sensitive Na^+ channels causing an entry of Ca^{2+} and therefore an increase of the cytoplasmic Ca^{2+} concentration; (2) the activation of guanylate cyclase by Ca^{2+} (or the inhibition of a phosphodiesterase); (3) the repression of AChR synthesis by cyclic GMP. Thus, both Ca^{2+} and cyclic GMP would correspond to the previously postulated 'shut off' factors¹⁴.

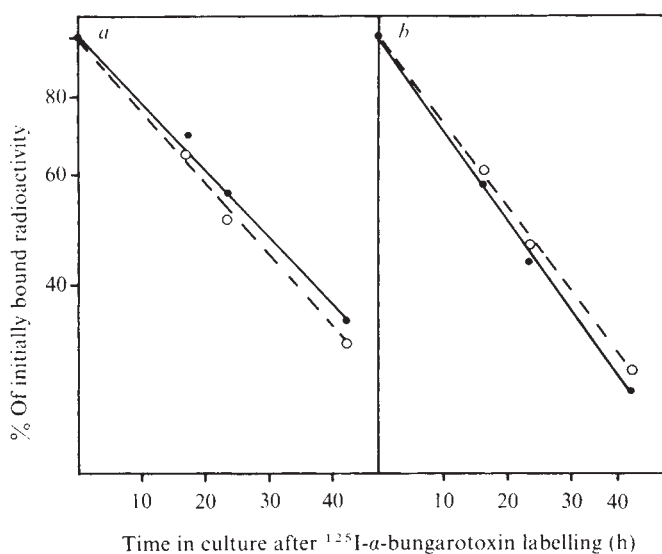


Fig. 3 Loss of ^{125}I - α -bungarotoxin binding sites in muscle cultures treated with dibutyryl cyclic nucleotides. 2-d-old muscle cultures prepared as in Fig. 1 were pretreated for 42–50 h with $2 \times 10^{-4}\text{M}$ dibutyryl cyclic GMP or dibutyryl cyclic AMP, respectively. The treated and parallel control cultures were then labelled by the addition of ^{125}I - α -bungarotoxin to a final concentration of 10 nM . After 1 h at 37°C , the cells were washed free of unbound toxin and cultivated in new medium containing the indicated additions. At different time intervals, duplicate dishes were removed, and the amount of bound ^{125}I - α -bungarotoxin radioactivity was determined. *a*: ●, Control; ○, $2 \times 10^{-4}\text{M}$ dibutyryl cyclic AMP; *b*: ●, control; ○, $2 \times 10^{-4}\text{M}$ dibutyryl cyclic GMP.

Table 2 Effect of TTX, veratridine and dibutyryl cyclic nucleotides on protein synthesis of chick embryonic myotubes in culture

Culture condition	Trichloroacetic acid-insoluble radioactivity (c.p.m. per dish $\pm$ s.e.m.)
Control	3,438 $\pm$ 240
Veratridine	3,452 $\pm$ 249
TTX	3,352 $\pm$ 60*
Dibutyryl cyclic GMP	3,428 $\pm$ 98
Dibutyryl cyclic AMP	4,442 $\pm$ 478

7-d-old muscle cultures prepared as described in Table 1 were treated with the above listed reagents for 20 h (concentrations identical to those listed in Table 1b); after 15 h, medium and additions were renewed. Then ^{35}S -methionine was added to the medium to a final concentration of $3 \mu\text{Ci ml}^{-1}$, and incorporation was allowed to proceed for 2 h. The cells were washed twice with phosphate-buffered saline, extracted in 1 M NaOH containing 5 mM L-methionine, and the trichloroacetic acid-insoluble radioactivity in aliquots of the extracts was determined by a glass fibre filter assay procedure. Number of dishes $n = 4$ or 5 except * $n = 2$.

As far as the effect of cyclic AMP and its derivatives is concerned, the following physiological implications might be considered. First, in cultures of myoblasts the level of intracellular cyclic AMP reaches a peak level shortly before fusion²⁵. The activation of adenylate cyclase may thus be essential for the coordinated induction of differentiated functions, including AChR synthesis in post-fusion myotubes²³. Second, our finding that AChR synthesis is regulated by compounds such as PGE_1 which change the intracellular levels of cyclic AMP offers a new approach to the old problem of 'neurotrophic' control of extra-synaptic acetylcholine sensitivity. Many extracellular factors may modulate the intracellular pool of cyclic AMP and thus superimpose on the cyclic GMP-mediated regulation of AChR by myofibre activity. The suppression of ACh supersensitivity by neural factors other than the neurotransmitter may, for example, result from the secretion of substances which inhibit adenylate cyclase (for example, insulin-like molecules) by the respective motor nerve terminals. In any case, the modulation of AChR levels by changes in the intracellular concentration of cyclic AMP probably represents a non-selective regulatory mechanism which may be connected with the general differentiation and maintenance of myofibre properties.

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HEINRICH BETZ

JEAN-PIERRE CHANGEUX

Neurobiologie Moléculaire,
Institut Pasteur,
Paris, France

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Activation of steroid hormone–receptor complexes in intact target cells in physiological conditions

AT physiological temperatures glucocorticoids^{1–5}, in common with other steroid hormones⁶, initially interact with normal target cells such as the rat thymocyte by forming hormone–receptor complexes that seem first to be located in the cytoplasm and then rapidly become bound to the nucleus. At low temperatures (0–4 °C) the hormones, when incubated either with target cells or with cytosols from such cells, form 'non-activated' complexes that do not bind to nuclei; subsequent warming of the cells^{1–5}, or of the cytosols together with nuclei^{2,7–11}, leads to the formation of nuclear-bound complexes. As shown originally with oestrogens¹² and later with glucocorticoids^{2,7–10,13}, if cytosols with non-activated complexes formed at 0–4 °C are warmed to 20–37 °C in the absence of nuclei, the complexes become 'activated', and will then bind to nuclei even at low temperatures. Activation, which can also be brought about by increased ionic strength^{7–9,13}, gel filtration, dilution and other treatments¹⁴, has been studied extensively and is known to be accompanied by several changes other than enhanced affinity for nuclei. For glucocorticoid–receptor complexes the changes include enhanced affinity for DNA^{7,10,13–15} and altered mobility on phosphocellulose¹⁶, DEAE-Sephadex¹⁷ and DEAE-cellulose¹⁸ columns. This last property is the one we have used in our experiments. Despite the many published studies on activation, formation of non-activated complexes and subsequent activation have apparently never been demonstrated in cells or cytosols exposed to steroids at normal body temperatures only. Consequently, it is not known whether non-activated complexes and activation have any significant role in physiological conditions, and at least one well known scheme of steroid hormone action¹⁹ does not include the activation step. It is therefore possible that when steroid hormones bind to cytoplasmic receptors at physiological temperatures they immediately form activated complexes. The results described here show that for glucocorticoids this alternative can be excluded: when these steroids interact with receptors in rat thymus cells at 37 °C they initially form non-activated complexes, and subsequently give rise to activated complexes.

Thymus cells from adrenalectomised rats were prepared and incubated in Krebs–Ringer bicarbonate buffer (0.3–0.4 ml packed cells per ml cell suspension) with radioactive steroids using procedures described elsewhere²⁰. Cytosols containing the cytoplasmic steroid–receptor complexes from these cells were

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obtained as supernatants following centrifugation (10 min, 2,000g, 3 °C) of broken-cell preparation obtained by diluting the cell suspensions sixfold in 1.5 mM MgCl₂ at 0–3 °C (refs 4, 5, 21). The MgCl₂ solution contained dextran-coated charcoal to adsorb free steroid^{5,21}. DEAE cellulose columns (0.7 cm diameter, 6 ml bed volume) were prepared with Whatman DE-52 cellulose that had been degassed under vacuum while suspended in 300 mM KH₂PO₄ and then washed with starting buffer (5 mM potassium phosphate, pH 7.4, with 0.5 mM dithiothreitol). All column procedures were carried out at 3 °C. Cytosols were applied as 0.7-ml aliquots. Each column was first eluted with 15 ml starting buffer to remove free steroid. This was followed by a 120-ml linear gradient from 5 mM to 300 mM potassium phosphate (pH 7.4) with 0.5 mM dithiothreitol¹⁸. The eluates were collected in 3-ml fractions, from which aliquots were taken for assay of radioactivity. Recovery in the eluates was 85–100% of applied radioactivity.

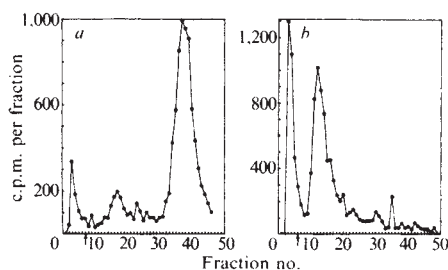


Fig. 1 DEAE-cellulose chromatography of cytosols containing predominantly non-activated (a) and activated (b) dexamethasone–receptor complexes. For the non-activated complex a cytosol was prepared from rat thymus cells incubated for 120 min with 7 nM [6,7-³H(N)]dexamethasone (specific activity, 33–40 Ci mmol⁻¹, NEN) at 0 °C, and chromatographed as described in the text. For the activated complex a similar cytosol was chromatographed after warming for 15 min at 25 °C. Numbers on the ordinate give the c.p.m. in the 3-ml fractions. The arrows on the abscissae indicate the start of the gradient elution. The peak to the left of the arrow, which probably consists of free steroid, was eluted with starting buffer.

The results in Fig. 1 on non-activated and activated ³H-dexamethasone–receptor complexes from rat thymus cells confirm and extend the results of Sakaue and Thompson¹⁸ on triamcinolone acetonide–receptor complexes from cytosols of rat liver, thymus and other tissues. As in their experiments the unwarmed cytosol, containing predominantly non-activated complex, gives a major peak on DEAE-cellulose chromatography that is eluted late in the gradient (fractions 31–45; following Sakaue and Thompson, we refer to this peak as Peak II). After warming to 25 °C for 15 min the cytosol gives a major peak eluted early (fractions 8–20; Peak I). The peak eluted with starting buffer (from fraction 0 to the arrow, Fig. 1) probably consists of unbound steroid, as the material in these fractions is adsorbed by dextran-coated charcoal, and in contrast to receptor-bound steroid does not bind to hydroxyapatite²². If the initial incubation with ³H-dexamethasone includes 10⁻⁶ M unlabelled dexamethasone, Peaks I and II disappear and the peak eluted with starting buffer is diminished. Sakaue and Thompson¹⁸ found that the steroid–receptor complex in Peak I binds much more efficiently to nuclei, chromatin and DNA-cellulose than that in Peak II; consistent with this, we have previously found that the complexes in warmed cytosols bind more efficiently to nuclei and DNA-cellulose than those in unwarmed cytosols^{2,15}. Our observations thus support Sakaue and Thompson's conclusion that Peaks I and II, respectively, represent activated and non-activated complexes.

The question of whether non-activated complexes are formed in physiological conditions can therefore be reduced to whether the complex initially formed when thymus cells at 37 °C are exposed to dexamethasone is eluted on DEAE-cellulose columns as the non-activated Peak II or as the activated Peak I.

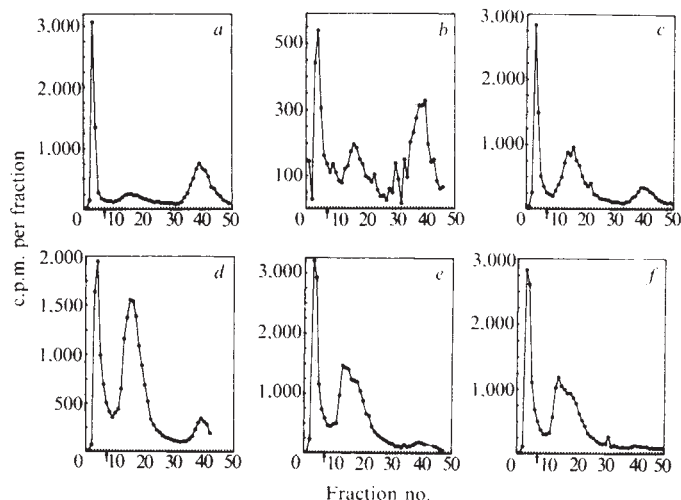


Fig. 2 Time course of formation of non-activated and activated dexamethasone–receptor complexes in rat thymus cells at 37 °C after addition of ³H-dexamethasone. Rat thymus cells incubated at 37 °C were exposed to ³H-dexamethasone for the times indicated. Incubations were terminated by a sixfold dilution of the cell suspension in 1.5 mM MgCl₂ at 0 °C, after which cytosols were prepared and chromatographed on DEAE-cellulose columns as described in the text. Each time of exposure represents a separate experiment, with free ³H-dexamethasone at concentrations of 50–100 nM. Ordinates and abscissae have the same meaning as in Fig. 1. Activated and non-activated complexes are associated, respectively, with the peaks at fractions 10–20 (Peak I) and 30–50 (Peak II). a, 0.25 min; b, 1 min; c, 2.5 min; d, 5 min; e, 15 min; f, 30 min.

The results in Fig. 2, which we have obtained consistently in several such experiments and have also confirmed using ³H-cortisol, show clearly that the non-activated complex is the first to appear. It is almost the only form present after 0.25 min, but is rapidly replaced over the next few minutes by activated complex and after 30 min is nearly undetectable. Figure 2 gives only the relative amounts of Peak I and Peak II at each time, but we have previously shown that in these conditions total cytoplasmic complex, that is, the sum of Peaks I and II, is formed with a half-time of about 1 min and reaches a fairly steady level by 5 min (ref. 5).

Thus, we conclude that the non-activated complex does have an important role in physiological conditions, apparently serving even at 37 °C as an obligatory intermediate in the initial formation of activated complex. In addition, the experimental approach shown in Fig. 2 provides kinetic and steady-state parameters on receptor transformations in intact cells that must be satisfied by any realistic model of receptor activation. Most models to date have been based on results obtained with cell-free systems. For example, it may be difficult to reconcile our results with a recent model of reversible activation, based on experiments with rat liver cytosols. In these, glucocorticoid–receptor complexes reach equilibrium with approximately equal amounts in the non-activated and activated forms, the latter form assayed by ability to bind to nuclei^{23,24}. In this connection, we have preliminary results suggesting that Peak I contains a minor component with little affinity for DNA-cellulose; we do not yet know whether this component is an experimental artefact or a third normal form of the cytoplasmic complex.

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ALLAN MUNCK

ROSEMARY FOLEY

Department of Physiology,
Dartmouth Medical School,
Hanover, New Hampshire 03755

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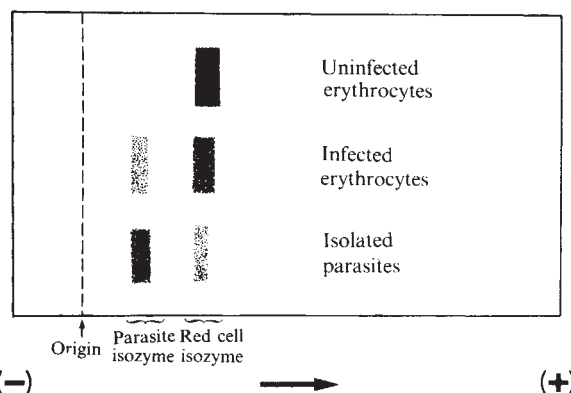


Fig. 1 Schematic representation of starch gel electrophoresis of lysates derived from normal and *P. berghei*-infected mouse erythrocytes and from isolated *P. berghei* parasites. Gels were stained for glutathione reductase (GR) activity with 2,6-dichlorophenol indophenol (DCIP) and 3-(4,5-dimethyl-thiazolyl-2)-2,5-diphenyl tetrazolium (MTT) in the presence of NADPH and GSSG¹⁵. Simultaneous staining of the other half of the gel with DCIP and MTT in the presence of NADPH but in the absence of GSSG resulted in no detectable staining, confirming that these isozymes represent GR. Note the appearance of a novel isozyme of GR in lysates from isolated parasites. The small amount of residual host cell GR in the latter sample is probably due to contamination of the isolated parasites with trapped host cell cytoplasm.

P. berghei (NYU-2 strain) was maintained in male Swiss White mice as previously described⁷. Blood from heavily infected mice (>70% of red cells infected) was collected after ether anaesthesia by axillary incision and aspiration into heparin. White cells and platelets were removed by filtration through powdered cellulose columns¹⁰. GSH¹¹ and glutathione reductase¹² were assayed as before.

P. berghei infected erythrocytes had more than twice the GSH content of uninfected red cells (Table 1). This difference was not an artefact due to changed size or haemoglobin content of

Dependence of plasmodial glutathione metabolism on the host cell

ONE inherited alteration of human red cell metabolism—quantitative deficiency of the X-linked enzyme glucose-6-phosphate dehydrogenase (G-6-PD)—has attained high frequency in many areas of endemic malaria and may protect against fulminant *Plasmodium falciparum* in some unknown fashion¹⁻⁵. G-6-PD catalyses the first step of the pentose phosphate pathway which provides reduced NADPH necessary for conversion of oxidised to reduced glutathione (GSSG → GSH)⁶. Erythrocytes deficient in G-6-PD are inefficient in generating NADPH and, when exposed to oxidants, lose GSH, accumulate oxidised haemoglobin and are destroyed by the reticuloendothelial system⁶. We hypothesised that, if the malaria parasite were to use red-cell NADPH for parasitic functions, the G-6-PD-deficient erythrocyte might be incapable of maintaining adequate GSH content. This would predispose the cell to premature destruction before the parasite matured, thereby limiting the severity of infection⁷⁻⁹. In exploring this hypothesis, we have investigated factors affecting GSH metabolism in malaria-infected mouse erythrocytes. We find that *P. berghei* malaria may utilise host-cell NADPH for the maintenance of parasite GSH. These observations may help elucidate both the parasite-induced red cell oxidant damage⁷ and the mechanism whereby G-6-PD deficiency protects against fulminant malaria infection.

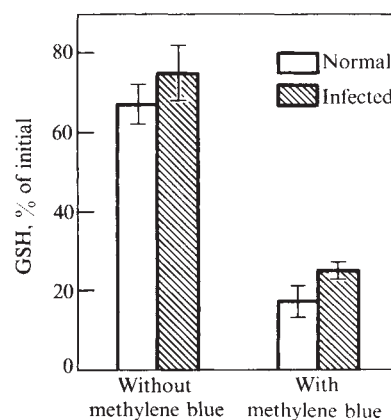


Fig. 2 Regeneration of GSH in whole erythrocytes previously treated with diamide. Suspension of uninfected and infected erythrocytes, haematocrit approximately 2 volumes per cent, were incubated with 0.25 mM diamide in 0.154 M NaCl for 30 s at 4 °C and washed in 0.154 M NaCl. Diamide-treated cells were resuspended to an haematocrit of approximately 2 volumes per cent in Hank's balance salt solution with 20 mg ml⁻¹ glucose, pH 7.4, with and without 500 μM methylene blue. Results are expressed as per cent of initial GSH concentration and represent the mean ± s.e.m. for 11 separate determinations.

infected cells and was apparent whether GSH concentrations were expressed per g haemoglobin, per ml packed red cells (Table 1) or even per 10^{10} red cells (data not shown). Nor was the difference explicable on the basis of decreased red cell age; our *P. berghei* infections last only 5–6 days from inoculation to death with no significant elevations in reticulocyte count.

To explore the possibility that the incremental GSH within infected cells might be parasite rather than erythrocyte GSH, we separated host cell cytoplasm from intact parasites by ammonium chloride lysis¹³. GSH analyses revealed that infected red-cell cytoplasm had normal GSH content, whereas isolated parasites contained most of the GSH found in whole infected cells (Table 1). We then investigated how the glutathione within the parasite might be maintained in the reduced state. Glutathione is constantly being oxidised and the reduction of GSSG to GSH is catalysed by glutathione reductase (GR), for which NADPH is the most important and, perhaps, sole substrate⁶.

Table 1 Concentrations of GSH and activity of glutathione reductase in uninfected and *P. berghei*-infected mouse erythrocytes, and in isolated parasites and host-cell cytoplasm separated by ammonium chloride lysis¹⁴

Group	N	GSH	
		μM per g Hb	μM per ml RBC
Uninfected red cells	20	5.6 (± 0.2)	1.9 (± 0.1)
Infected red cells	16	16.3 (± 1.5)*	3.9 (± 0.3)*
Group	N	Glutathione reductase (GR)	
		IU per g Hb	IU RBC
Uninfected red cells	15	14.7 (± 0.6)	4.6 (± 0.2)
Infected red cells	11	35.4 (± 4.0)*	7.8 (± 0.5)*

		GSH	GR
		μM per g protein	IU per g protein
Isolated parasites	10	12.0 (± 0.4)	15.5 (± 0.7)
Infected red cell cytoplasm	10	5.6 (± 0.3)	20.9 (± 2.3)

Figures in parentheses represent 1 s.e.m. Because the assay which we routinely use for GSH analysis utilises 5,5-dithiobis(2-nitrobenzoic acid) (DTNB), which may detect other reducing substances, we confirmed the identity of the GSH in infected cells and isolated parasites by chromatography on Biogel P-2 which showed that >95% of the DTNB reacting substance had a molecular weight similar to GSH.

* $P < 0.001$ when compared to values from uninfected red cells (Student's *t* test, two tailed).

Comparison of NADPH-dependent GR activities within uninfected and infected erythrocytes revealed marked increases within infected cells (Table 1). Although some mammalian forms of GR may use NADH as cofactor¹⁴, even at >1 mM NADH we were unable to detect GSSG reduction by either parasite or host cell GR. Starch gel electrophoresis of lysates derived from normal and infected erythrocytes, and from isolated parasites, indicated the presence of a unique parasite GR cathodal to the single host-cell isozyme (Fig. 1). This isozyme of GR in infected red cells is unlikely to be a modified form of the host-cell enzyme because of the large increase in enzyme activity within infected erythrocytes. This increased activity could not be explained by diminished red cell age because, as indicated earlier,

our *P. berghei* infections do not induce reticulocytosis. Furthermore, others have reported similar elevations of both GSH and GR activity in mouse erythrocytes infected with an entirely different species of malaria—*P. vinckei*¹⁶.

However, the source of the NADPH required for the activity of parasite GR was not clear. *P. berghei* (and other forms of malaria), lacks detectable G-6-PD activity^{17–19} and is, therefore, unable to utilise an intact pentose phosphate pathway for the generation of NADPH. Despite this, pentose shunt metabolism is accelerated in parasitised erythrocytes ($5\text{--}10\times$ normal)^{20,21}, although the activity of this pathway is low or absent in the parasite itself¹⁸. These observations suggested that the parasite might be oxidising red cell NADPH, perhaps through NADPH-linked reduction of parasite GSSG. The excess NADP so generated would, predictably, accelerate the host-cell pentose shunt⁶. To test the possibility that parasite GSSG might be reduced by external NADPH, we isolated parasites¹³ and reversibly oxidised parasite GSH to GSSG with diazene-dicarboxylic acid-bis-(*N,N*-dimethylamide) (diamide)²². As shown in Table 2, following brief treatment of parasites with diamide, incubation with exogenous NADPH supports the regeneration of GSH. This GSH regenerated during incubation must occur within the parasite because extensive washing of parasites does not result in a significant decrement in GSH concentration. Note

Table 2 Regeneration of GSH in diamide-treated isolated *P. berghei*

Substrate	Number	GSH, % of initial
None	20	17 (± 6)
NADPH (500 μM)	30	67 (± 14)*
NADPH (50 μM)	6	58 (± 11)*
NADP (500 μM)	8	16 (± 8)
D-Glucose (11 mM)	8	17 (± 4)
G-6-P (500 μM)	6	18 (± 8)
6-PG (500 μM)	6	19 (± 7)
G-6-P (500 μM) + NADP (500 μM)	6	38 (± 12)
6-PG (500 μM) + NADP (500 μM)	6	43 (± 14)

Suspensions of isolated parasites, approximately 10 mg protein per ml, were incubated with 0.7 mM diamide in 0.154 M KCl containing 20 mM Tris buffer, pH 7.4, at 4 °C for 30 min. The parasites were then washed in the KCl-Tris buffer to remove the unreacted diamide and resuspended to a concentration of approximately 25 mg protein per ml in KCl-Tris buffer. GSH determinations were done before and immediately after diamide treatment, and after 60 min incubation with the various additives at 37 °C. In all experiments, the mean of the initial GSH concentrations was $11.2 \pm 0.3 \mu\text{M}$ per g protein and GSH was undetectable immediately following diamide treatment. Results are expressed as per cent of initial GSH and represent the mean ($\pm$ s.e.m.).

*Significantly different from control (no substrate) at $P < 0.001$ by Student's *t* test, two tailed.

that even NADPH concentrations of 5×10^{-5} M (somewhat below the levels found in normal human erythrocytes⁶) will support reduction of intraparasitic GSSG. The failure of the GSH concentration to return to 100% of the initial values is probably due to diamide-induced damage to the parasite as well as possible loss of GSSG during diamide treatment. The glutathione reduction is specific for NADPH; incubation of isolated parasites with glucose, NADP, glucose-6-phosphate (G-6-P), or 6-phosphogluconate (6-PG) results in no reduction of GSSG (Table 2). Samples incubated with both NADP and G-6-P or 6-PG do regenerate some GSH (Table 2), possibly mediated by host cell G-6-PD and 6-phosphogluconate dehydrogenase which, like other components of host cell cytoplasm, unavoidably contaminate preparations of isolated parasites.

Other observations indicate that the parasite is directly dependent on erythrocyte metabolism for reduction of GSSG.

In diamide-treated intact infected erythrocytes, glucose supports the regeneration of GSH (Fig. 2) within both host-cell cytoplasm and parasite (data not shown). In contrast, similar incubation of diamide-treated isolated parasites with glucose results in negligible reappearance of GSH (Table 2). Finally, parasite GSSG reduction within whole infected erythrocytes also appears to require NADPH. As shown in Fig. 2, methylene blue (which oxidises intracellular NADPH to NADP^{23,24}) blocks GSSG reduction in intact normal and infected erythrocytes incubated with glucose.

The utilisation of exogenous NADPH for the reduction of parasite GSSG to GSH, as well as the inability of isolated parasites to use glucose for this purpose, indicates an intimate metabolic dependence of the parasite upon the host red cell. The attendant oxidation of erythrocyte NADPH during reduction of parasite GSSG may explain both the increased oxidant sensitivity of infected erythrocytes, and the acceleration of pentose shunt activity within infected cells^{21,22}. Our results also suggest a mechanism whereby G-6-PD deficiency may protect against fulminant malaria infection. The utilisation of NADPH by both the host erythrocyte and malaria parasite would overwhelm the limited ability of G-6-PD deficient red cells to regenerate NADPH. The resultant decrement in cellular GSH may predispose the infected erythrocyte to premature, oxidant-induced destruction. Alternatively, the accumulation of GSSG may inhibit parasite protein synthesis²⁵. In either case, the reliance of the malaria parasite on host-cell NADPH may represent a site of action for new antimalarial drugs.

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JAMES R. ECKMAN*

JOHN W. EATON

Department of Medicine,
University of Minnesota,
Minneapolis, Minnesota 55455

Received 28 December 1978; accepted 20 February 1979.

*Present address: Department of Internal Medicine, Emory University, Atlanta, Georgia 30303.

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Homogeneous sensitivity of human peripheral blood lymphocytes to radiation-induced chromosome damage

THE routine method for detecting genetic damage induced by environmental agents in man *in vivo* is to examine mitotic cells in short-term peripheral blood lymphocyte cultures for evidence of structural chromosome changes^{1,2}. Chromosome radiosensitivity in lymphocytes irradiated *in vivo* and *in vitro* is similar³, and so dose-response relationships have been established for different qualities and quantities of ionising radiations after *in vitro* exposure of blood samples⁴. These curves are used to estimate doses received in cases of accidental overexposure to radiation^{1,2,5} and in prediction of the sensitivity of human germ cells to heritable radiation damage⁶. Their shape is used to predict the effect of dose rate on chromosome aberration frequencies^{7,8} and to elucidate the mechanisms of induction of

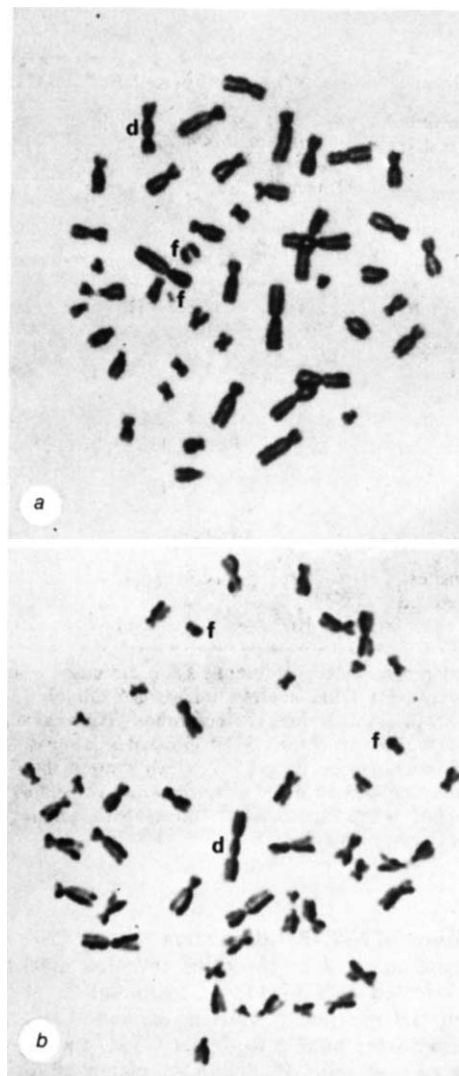


Fig. 1 Metaphase cells at first (a) and second (b) mitosis after exposure of whole blood to 200 rad of X rays, incubation in medium containing BUdR, and harlequin staining¹². d = dicentric, f = fragment. The harlequin-stained cell in second metaphase carries a dicentric and two identical fragments derived from duplication of a single fragment at first mitosis.

Table 1 Dicentric frequencies and proportions of metaphase cells which have undergone more than one mitosis at different times after initiation of blood cultures from four donors

Donor	Treatment	Fixation time(h)	Metaphase cells at >1st division (%)	Dicentrics per 100 cells:			Poisson distribution of dicentrics in 1st divisions? χ^2 test, $P =$
				1st Mitoses	2nd Mitoses	All mitoses (not harlequin stained)	
A	200 rad + BUdR	40	3	48			0.70–0.80
		44	2	50			0.50–0.70
		48	2	54			0.10–0.20
		56	22	55			0.80–0.90
		60	35	55			0.50–0.70
	200 rad	40			26	52	
		44				53	
		48				53	
	BUdR	52	17			0	
		52				0	
A	200 rad + BUdR	48	2	43			0.02–0.05*
		56	30	43			0.20–0.30
		64	55	43	28		0.50–0.70
		72	73	43	20		0.50–0.70
		48				38	
	200 rad	48				0	
		72	85			0	
		64				0	
	BUdR	44				0	
		48				0	
B	200 rad + BUdR	44	0	36			0.50–0.70
		48	0	40			0.20–0.30
		52	20	47			0.70–0.80
		56	19	43			0.90–0.95
		60	34	41	14		0.30–0.50
	200 rad	68	57	35	21		0.90–0.95
		44				38	
		48				44	
	BUdR	52	11			1	
		52				0	
C	200 rad + BUdR	48	2	44			0.10–0.20
		56	23	44			0.98–0.99
		64	59	45	29		0.20–0.30
		48				35	
		72	90			0	
	200 rad	64				0	
		48				0	
		72				0	
	BUdR	48				0	
		64				0	
D	200 rad + BUdR	48	2	43			0.98–0.99
		56	20	43			0.90–0.95
		64	57	42	22		0.90–0.95
		72	70	41	27		0.80–0.90
		48				44	
	200 rad	72				0	
		48				0	
		64				0	
	BUdR	72	79			0	
		64				0	

Each value is derived from an analysis of 100 cells.

* A significant departure from a Poisson is expected by chance in the total of 22 samples analysed in these experiments.

such aberrations⁸. However, accurate dose–response curves can be obtained only if cells are examined for chromosome damage at the first post-irradiation mitosis, because aberrations decline with successive divisions⁹. Crossen and Morgan¹⁰ used the harlequin-staining technique^{10,12} on phytohaemagglutinin (PHA)-stimulated lymphocytes exposed to bromodeoxyuridine (BUdR) to distinguish cells at first and later mitoses *in vitro* (Fig. 1). They have shown that at the conventional sampling time, about 48 h after stimulation, up to 53% of cells may be in second mitosis. Another problem is that the cells examined in first division at 48 h may not be representative of the entire cell population. Several workers^{13–15} have claimed that lymphocytes with different rates of response to PHA stimulation, undergoing first mitosis at different times after stimulation, carry different frequencies of aberrations. They have interpreted this as a sign that lymphocytes in the peripheral blood constitute a heterogeneous population in terms of chromosome radiosensitivity. If this were true, little significance could be attached to the shape of the dose–response curves. We report here that we have used the harlequin technique to show (1) that in spite of radiation-induced mitotic delay¹⁶ high frequencies of cells in second mitosis may still be found at 48 h, and (2) that there is no difference in aberration frequency in first-division cells sampled at various intervals after irradiation. Correct dose–response curves can therefore now be obtained with this method and any sampling time can be used provided that observations are confined to non-harlequin-stained (that is, first division) cells.

In preliminary experiments, X-ray-irradiated or non-irradiated blood samples were cultured in medium containing BUdR

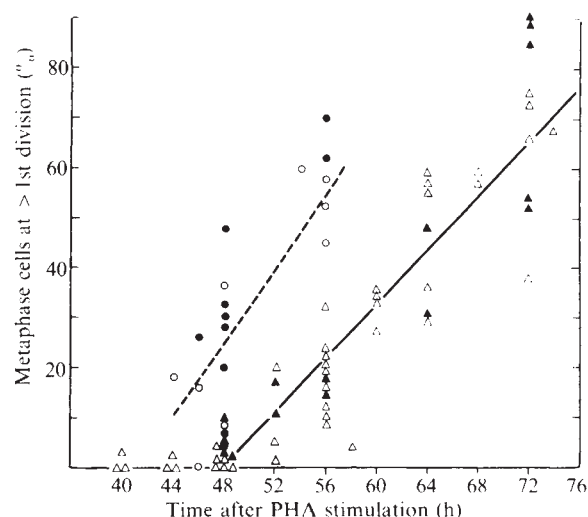


Fig. 2 Proportions of metaphase cells which have undergone more than one mitosis at different times after initiation of cultures of irradiated (150–300 rad of X rays) or non-irradiated blood. Distinction between cells at first or later mitoses was made after harlequin staining¹² of cells grown in medium (80% Hams F10 + 19% fetal calf serum + 1.0% PHA) containing BUdR at 5 or 10 $\mu\text{g ml}^{-1}$. Cells were exposed to colcemid for 1 h before fixation. Data are from several experiments in which blood from six male donors (aged 21–33 yr) was used. Each point represents the analysis at 100 metaphase cells. Solid and dashed lines have been fitted by eye to the data for BUdR at 10 $\mu\text{g ml}^{-1}$ and 5 $\mu\text{g ml}^{-1}$, respectively. ●, non-irradiated, BUdR 5 $\mu\text{g ml}^{-1}$; ▼, non-irradiated, BUdR 10 $\mu\text{g ml}^{-1}$; ○, irradiated, BUdR 5 $\mu\text{g ml}^{-1}$; △, irradiated, BUdR 10 $\mu\text{g ml}^{-1}$.

at either 5 or 10 $\mu\text{g ml}^{-1}$, fixed at various times after culture initiation and harlequin stained. After 5 $\mu\text{g ml}^{-1}$, up to 48% of cells were in second mitosis by 48 h (Fig. 2) and 37% even after 300 rad of X rays. BUdR evidently induced some mitotic delay because the frequencies of cells beyond first division (Fig. 2) were, in general, considerably lower after 10 $\mu\text{g ml}^{-1}$ than after 5 $\mu\text{g ml}^{-1}$ (ref. 17). This suggests that in normal culture conditions, without BUdR, there may be even more than 50% of cells at second division by 48 h. Because the magnitude of mitotic delay is dose dependent¹⁶ there will be, at 48 h, a decreasing proportion of cells in second division with increasing dose, which will lead to an exaggeration of the curvature of the dose-response curve when the BUdR method is not used.

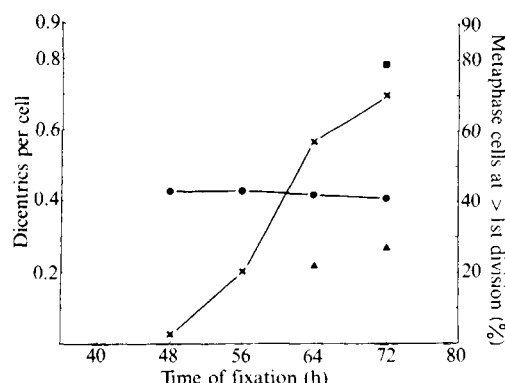


Fig. 3 Dicentric frequencies in cells from donor *D* (see Table 1) at first (●) and second (▲) mitosis after exposure to 200 rad of X rays. Also shown is the proportion of cells at >1st mitosis (×, irradiated; ■, control) at different sampling times.

To investigate aberration frequencies in first-division cells at different sampling times, whole blood from four healthy male donors (aged 21–33 yr) was exposed to 200 rad of X rays (290 kV, 8 mA, 100 rad min⁻¹) at 37°C, cultured in medium with 10 $\mu\text{g ml}^{-1}$ BUdR, sampled between 40 and 72 h and harlequin stained. Non-irradiated cells were exposed to 10 $\mu\text{g ml}^{-1}$ BUdR or no BUdR, and some irradiated cells were cultured without BUdR. The results are shown in Table 1 and Fig. 3. There was no significant difference between sampling times in aberration (dicentric) frequencies in first-division cells (donor *A*, first experiment, $\chi^2_4 = 0.79$, $P = 0.90$ – 0.95 ; donor *A*, second experiment, $\chi^2_3 = 0$, $P = 1.0$; donor *B*, $\chi^2_5 = 2.46$, $P = 0.70$ – 0.80 ; donor *C*, $\chi^2_2 = 0.08$, $P = 0.95$ – 0.98 ; donor *D*, $\chi^2_3 = 0.063$, $P > 0.99$). BUdR did not induce aberrations (compare BUdR treatment with no treatment in Table 1). As in our preliminary studies (Fig. 2), with 10 $\mu\text{g ml}^{-1}$ BUdR the frequency of second divisions at 48 h was low. BUdR did not influence the frequency of aberrations induced by radiation (compare 200 rad only with 200 rad + BUdR at early fixation times before onset of second mitosis). Dicentric frequencies in second-division (harlequin-stained) cells were approximately half those in first-division cells, as expected if (1) 50% of dicentrics form bridges at first anaphase and 50% “fall-free” (ref. 18), and (2) cells with or without dicentrics at first mitosis are equally capable of undergoing second division. The means of the dicentric frequencies at all sampling times in first division cells from donors *A* (second experiment) *B*, *C* and *D* were similar, being 43.0, 40.3, 44.3 and 42.3 per 100 cells, respectively, but the frequency from donor *A* in the first experiment (52.4 per 100 cells) was significantly higher than these at the 5% significance level. The reason for this is not clear and repeat samples from the other donors will be required to assess the importance of this observation.

The distribution of dicentrics between first division cells at each fixation time conforms to a Poisson distribution (Table 1).

This provides further evidence of homogeneity of lymphocytes in chromosome radiosensitivity other than the equality of aberration yields in first-division cells at different sampling times.

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D. SCOTT
C. Y. LYONS

Paterson Laboratories,
Christie Hospital & Holt Radium Institute,
Manchester, UK

Received 7 December 1978; accepted 26 February 1979.

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Corrigendum

In the letter ‘Nanosecond transient Raman spectra of photo-lysed carboxyhaemoglobin’ by K. B. Lyons *et al.*, *Nature* **275**, 565–566 (1978), paragraph 6 line 15 and paragraph 8 line 6 reads 0.002 Å not 0.02 Å. On Fig. 1c 3 cm⁻¹ should read 2 cm⁻¹.

Erratum

The following note in proof should have appeared in the Matters Arising item ‘Synergistic chelation therapy or mixed ligand complexes for plutonium and cadmium poisoning?’ by P. M. May and D. R. Williams, *Nature* **278**, 581; We would like to correct an error in our *Nature* paper⁴. In paragraph 4 and in Fig. 3 legend we reported that tablets of EDTA with salicylate or DNPS (Dimaval) protected mice from acute cadmium poisoning given 1 h post-cadmium. This should have read 5 min rather than 1 h as far as complete survival is concerned. Naturally, complete survival is observed 15 min but not 1 h post-cadmium for a single injection of the combination.

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reviews

Physics as natural philosophy

Victor F. Weisskopf

Memoirs of a Physicist in the Atomic Age. By W. M. Elsasser. (Adam Hilger: Bristol, 1978.) \$15.

I HAVE rarely read a memoir of a scientist which is as readable and captivating as this one. Scientists are not usually very good writers, but Walter Elsasser is. My judgement may be biased, as I belong to the same generation of scientists of Jewish origin brought up in the pre-Nazi German environment. The book gives a fascinating and tragic description of his slow and painful recognition as a young man that he did not belong to the society in which he grew up, although its cultural values were deeply ingrained in his thinking and feeling. In some ways he remained German all his life in the sense of Bach, Goethe, Schiller, Beethoven, Helmholtz and Freud. I think this is mainly why Elsasser keeps returning throughout the book to his belief that science should be natural philosophy and not a pragmatic study of nature. He has never felt comfortable in the Anglo-Saxon (or perhaps more typical, American) style of scientific research, although it is not as far from his ideal as he makes out.

In spite of its readability the book has a few shortcomings which will disappoint historians of science. Elsasser was in Göttingen at the time when quantum mechanics was beginning to take shape, but very little can be found in the book of the overwhelming excitement that must have been felt there, or of the discussions between Max Born, Pascual Jordan, James Franck and many others about the foundations of quantum mechanics. Also, too little is said about the enormous influence of Niels Bohr on the development of atomic physics at that time.

Elsasser did not have a happy life. In contrast to many other scientist-refugees, he did not become a full professor at a great university until the very end of his life. He had to work in industrial and governmental laboratories on subjects that were not his own choice, despite the fact that he was the person who initiated important insights into three of the most fundamental problems of physics: the interpretation of the results of the



Elsasser in 1974

Davisson-Kunsman (later Davisson-Germer) experiments as an effect of electron waves; the recognition of a shell-structure in atomic nuclei; the explanation of the Earth's magnetism as a self-generating dynamo in a liquid iron core. All three contributions were published as short notes: they were great flashes of ideas; and it was not Elsasser's style to elaborate details. Indeed, his note on the shell-structure of nuclei was all but forgotten when M. Mayer and H. Jensen rediscovered it 15 years later. They worked it out in detail and received the Nobel prize for their work.

These three contributions of Elsasser should have sufficed to secure him a high position in the scientific community. But he had bad luck all through his life as regards the recognition of his ideas and to his professional career—caused not only by external circumstances but also by his own personality. Elsasser was a difficult and complex character; he describes vividly some of the severe psychological troubles which he encountered in his youth. In spite of all these hardships he never lost his idealism and his devotion to what he calls "conceptual thought"—his interest in the essential and fundamental questions of science rather than in problem solving or empirical data collection.

Perhaps his lack of social success in the scientific community made him supercritical of some personalities and of the character of modern science. He describes the personality of P. Ehrenfest in such dark colours that he is not

recognisable to anyone who had personal contact with this warm-hearted, engaging and stimulating man. It is true that Ehrenfest was sometimes subject to moody periods; obviously a collision happened here between two difficult characters, that prevented Elsasser from recognising the unique humanity and charm of Ehrenfest. Also Hermann Weyl is censured because of his alleged lack of contact with reality in his books on relativity; an accusation which is in no way justified. Homi Bhabha too gets a rather heavy censure when he is accused of "modelling the properties of elementary particles in mathematical terms" and of trying to solve fundamental problems with inadequate means, as many of "those who come from cultures far from the circle of modern Western rationalism". Actually, Bhabha's contributions to particle physics were at least as fundamental as those of any Western physicist.

Elsasser was very much interested in the scientific explanation of the phenomena of life, and was very sceptical as to the possibility of a physico-chemical explanation. He wrote three books about the subject, and had to modify his point of view to some extent after the discovery of the DNA double helix. But it is not easy to understand why he found it necessary to denigrate the importance and impact of Schrödinger's pioneering little book *What is Life?*, which has influenced a whole generation of biologists. Elsasser had a very high opinion of Schrödinger in every other respect. But he completely overlooked the fact that Schrödinger introduced for the first time the concept of an "aperiodic crystal", which was later found to exist in the form of DNA. Also, Elsasser seems to assume that the book was written after the discovery of the genetic code.

Altogether the disappointments which Elsasser suffered within the scientific community must have accumulated many prejudices in his thinking. He goes as far as to accuse the life sciences as a whole of being a "denial of science as a creative activity". He says that "scientific research was a process in which observation was related by a reciprocal interaction with thought . . . but now it seemed that in

the life sciences the prevailing approach . . . has assumed a quite different form".

In physics, he could not approve of the attitude of the younger generation of scientists towards their work: "The modern physics that had emerged . . . was world apart from the old physics that had for so long been called natural philosophy". Although there may be some truth in what he says about the pragmatic attitude of modern science, his outright condemnation is fundamentally mistaken. The spirit that drives the best of the younger generation—always only the best ones are counted—remains the urge for deeper knowledge and insight into the workings of nature. Maxwell and Darwin would have appreciated modern science if they were still alive.

These exaggerated condemnations do not detract from the intrinsic value of the book. On the contrary, they appear as part of the author's personality and help to bring out the profound predicament of a person brought up in the highly literate and idealistic atmosphere of the well educated central European middle class, when confronted with the spirit (or non-spirit) of the last quarter of our century.

Many episodes during the War are related with great skill. His description of the tensions and problems in F. Joliot-Curie's laboratory during the

German occupation is thoroughly fascinating, as the laboratory served partly as a scientific institution and partly as a centre of the resistance. Unfortunately, he does not mention the heroic role of Professor W. Gentner, who was sent to the laboratory as a German caretaker but, at the risk of his life, kept a helping and protecting hand over Joliot-Curie and his group.

Many deep thoughts and ideas are presented in this book. Elsasser has never shied away from posing the hardest questions and was never discouraged by the difficulties of finding answers. The question of body and mind is often brought up in this book, always illuminating some aspects and indicating the vastness of the problem. Here is one revealing quote: "We tend to look with condescension and pity on that period of history, called the Middle Ages, when men were so concerned with their souls that they often ignored the external world. It seems today that most men are so embroiled in the external world that they have lost sight of the vast dimensions of the world of psyche."

It is a deeply moving book, with some weaknesses, but also with much of the glory that goes with the quest for scientific knowledge. □

Victor F. Weisskopf is Professor of Physics at the Massachusetts Institute of Technology, Cambridge, Massachusetts.

Life from extraterrestrial sources

Colin Pillinger

Lifecloud: The Origin of Life in the Universe. By Fred Hoyle and N. C. Wickramasinghe. Pp. 189 (Dent: London, Toronto and Melbourne, 1978; Harper and Row: New York, 1979.) £5.95; \$9.95.

OVER the past couple of years a number of articles have appeared in the scientific literature laying the ground work for the Hoyle and Wickramasinghe hypothesis that chemical evolution occurred deep in space in interstellar gas clouds rather than in a 'primeval soup' on the Earth. In the present book they suggest that even very complex biological molecules are produced in this way and contributed to the primitive Earth by cometary impact. They contend that all the comparatively volatile materials in the atmosphere and oceans and even living cells are derived from an extraterrestrial source.

Lifecloud may be summarised as follows. The first three chapters deal with aspects of Darwinian theory. Chapters 4, 5 and 6 provide basic introductions to the functions of cells, the structure of biochemicals and atomic theory, respectively. Chapter 7 discusses how stars are formed, whereas 8 includes a catalogue of the wide range of molecular species in interstellar space now identified by radioastronomy and 9 and 10 are devoted to speculation on the nature of the dust associated with the molecular clouds (mostly the authors' own proposal concerning cellulose). The next two chapters consider the structure of comets and the evidence for biological precursors in meteorites; then come chapters on the birth of the Solar System and the early history of the Earth. Chapters 15 and 16 examine other bodies in our Solar System or associated with the Sun's neighbours as possible abodes for life; Chapter 17 develops the philosophy of the predator in evolution; Chapter 18, entitled "Invasion from the galaxy", is not an appraisal of the much publicised suggestions by the authors that certain epidemic illnesses were brought to Earth by extraterrestrial viruses, but an evaluation of the feasibility of colonising the Universe by space travellers. From the last chapter it is clear that Hoyle and Wickramasinghe favour the armchair

approach of attempting radio communication as an essential first step in exploration.

From the format of the book, it is quite clear that the authors are not writing for specialist readers. The amount of introductory material included suggests that the intended audience may have only a general scientific background. This being the case, in my opinion, the authors should have felt a duty to distinguish clearly what is well founded evidence and what is speculation. Many of their readers will not be equipped to make such a judgement. Bearing in mind that the actual text of the book begins on p 15, and ends on p 174 and the large number of chapters (19) leads to numerous blank or semiblack pages, an attempt has been made to cover an amazing amount of material in probably less than 150 pages. This inevitably means that certain very controversial ideas are presented as fact.

Personally I would have preferred to see a much longer book, more conservatively written and critically reviewing alternatives where they exist. For example, a major theme of the book requires that interstellar dust be identified as cellulose or polysaccharides and spectral evidence is presented to this effect. Most radio astronomers would agree that it is not possible, at present, to decide unambiguously between cellulose and the numerous other materials which have been suggested. Similarly, alternative substances could be responsible for the 2200Å extinction attributed by the authors to $C_8H_8N_2$, but none are discussed. An interesting point, in this respect, is the strength of the evidence required for proof of chemical structure by different scientific disciplines. The organic chemist would consider infrared and ultraviolet spectra, insist on mass spectrometry, like to have nuclear magnetic resonance and attempt coinjection using two gas chromatographic phases. If a natural product was involved its stereochemistry would need to be examined. For some astronomers a near match between comparatively featureless spectra seems to be adequate. Whereas the chemist would concede the difficulties of obtaining data and material for study, perhaps the astronomer could afford to be a little more sceptical. There is a long way to go before the identification of $C_8H_8N_2$ confirms the existence of porphyrins such as $MgC_{16}H_{30}N_6$.

Several instances occur in the book when the evidence presented by the authors needs a much more careful scrutiny than seems to have been the case. On p31, while discussing the possibility of Precambrian microfossils, it is suggested that trace quantities of certain biochemicals have been found associated with the observed structures. No evidence exists to demonstrate that the chemicals in question are due to the microfossils rather than the host rock, whereas strong

Hoyle and Wickramasinghe



arguments favour an interpretation that the samples have been contaminated, not during collection or in the laboratory when great care is taken, but by geological processes. Precambrian rocks contain both classes of compounds and stereoisomers which thermodynamically could not have survived the $1-3 \times 10^9$ yr since rock consolidation. Several groups (for example, Nagy; *Geochim. Cosmochim.* **34**, 525; 1970) were able to show that the porosities of cherts were far in excess of what might be expected, and percolating ground water could easily have transported recently deposited chemical fossils into the Precambrian record.

In examining the clues from meteorites the authors are again guilty of using only selected evidence. The investigation of organic molecules in these extraterrestrial samples are so fraught with controversy that many investigators have declined to study them further. Of the extractable compounds, only the amino acids by virtue of stereochemical arguments may be considered to be indigenous to the samples. Since amino acids are racemic mixtures, it is impossible to decide whether they are biological, that is, associated with meteorite 'microfossils' (assuming you believe these are not organised elements) or the remnants of an abiogenic synthesis. Many of the other classes of compounds which may be extracted by organic solvents from meteorites could be terrestrial contamination. Han *et al.* (*Nature*, **222**, 364; 1969) have shown clearly that easily recognisable amounts of terrestrial organics were accumulated by samples of the carbonaceous chondrite Allende during only a few hours in the terrestrial environment. Like other naturally occurring polymers, the insoluble organic material associated with carbonaceous chondrites is not particularly well characterised despite many heroic efforts. It is generally agreed to be a highly aromatic substance but few would accept an identification as cellulose

on the basis of similarities in the infrared spectrum alone. Perhaps some of the efforts now underway to identify the host phases of isotopically anomalous rare gases in certain meteorites might be more successful in recognising pre-Solar System material. Although a number of possibilities are currently being entertained, cellulose is not among them.

The book contains a number of trivial but real errors. The authors are obviously confused by meteorite terminology. A "fall" is a meteorite observed to fall and later collected; a "find" is a meteorite discovered accidentally and identified as such by its mineralogy, petrology, chemistry etc. Thus (p108) 90% of all "falls" (not finds) are stone meteorites; because of their vulnerability to weathering all known carbonaceous chondrites are "falls" not finds. There are well in excess of 1500 (about 2300) well catalogued meteorites (again not falls) (p 18

and p 108); since the Antarctic bonanza of recent years a great many more samples have been discovered. Many physicists would not agree that the solar wind imprinted the lunar magnetic field (p137). Finally it is to be hoped that the authors' knowledge of chemistry is not accurately reflected by the alarming number of mistakes in the structure of chlorophyll as depicted on p 51 or their choice of glycine (an amino acid without an asymmetric carbon atom) as an example of an optically active molecule (Appendix 2).

Although from my comments it does not seem that I was over impressed with this book, I recommend reading it. I look forward to seeing a revised edition, as I am in agreement with some of the authors' overstated sentiments. □

Colin Pillinger is Senior Research Associate in the Department of Mineralogy and Petrology at the University of Cambridge, UK.

Acknowledging global links

Peter J. Smith

Cosmos, Earth, and Man: A Short History of the Universe. By P. Cloud. Pp. 372. (Yale University Press: New Haven, Connecticut, and London, 1978.) £10.75.

IN his Preface, Preston Cloud thanks "those anonymous critics of the several publishers who rejected an earlier draft of this book for their often cutting but nevertheless helpful comments". It is a gesture of characteristically Cloudian impishness, a humorous rounding-off to a piece of history that lesser people would rather have concealed. But joking apart, things have come to a pretty pass when one of America's best known Earth scientists can build up a collection of rejection slips and then only get published with the aid of a grant. In a market that publishers believe can support more than fifty practically identical general introductions to geology, it is nothing short of disgraceful to find a better book than most of them almost falling by the wayside.

For not only is Cloud a better stylist than most, he has a more original approach to content borne of a more original mind. His line is biogeology, which the American Geological Institute's *Glossary of Geology* defines as the "application of biological data to geology" but which in a lifetime of research Cloud has turned into something altogether more exciting than that dry definition would suggest. The advantage of having a foot in each

of two scientific camps is the acquisition of tendencies to spot connections and perceive correlations between developments parallel in time: and in *Cosmos, Earth, and Man* both are given rein. Where a pure anthropologist might see the ascent of man as a largely isolated phenomenon, Cloud relates man's evolution to the movement of continents, changes in climate and the encroachment of oceans:

"The breakup of the consolidated late Paleozoic continent of Pangaea, followed by the drifting apart of the pieces to form the present continents, set in motion a complex of processes that led to a general moderation of Mesozoic continental climates. Late Mesozoic changes and climatic deterioration that contributed to the extinction of the dinosaurs prepared the way for mammals to inherit the earth. Plate tectonics . . . may be related to the emergence of *Homo sapiens* . . ."

To be sure, our knowledge of global links is sparse and, where it exists, usually rather general. Nevertheless, it stands Cloud in good stead throughout the first three-quarters of his book where he works up from the nature of matter to space and planets, to the origin and evolution of the Earth and atmosphere, and to the origin of life and its evolution through plants and animals. It also helps in his discussion of the development of man; and up to this point the story that Cloud tells is as fascinating as some of the best fiction and surely has something new to impart not only to the layman, for whom the book is primarily intended, but also to all but the most erudite of Earth scientists. Up to this point, too, it has a convincing air of authority about it.

Unfortunately, perhaps, Cloud's pre-dilections and the logic of the global linkage concept then lead him on inexorably to consider the future of

Homo sapiens in the context of the impending ecological crisis which, as hundreds of books and articles have told us already, is serious precisely because of global interactions. But however sincerely meant, this is the least satisfactory part of the book, partly because it is difficult to find anything genuinely new to say and partly because Cloud ignores or underplays an essential part of the argument.

His general solution, shorn of all detail, is "strategic research and planning involving all sectors of society". He may be right; but even though he acknowledges that the growth of technology since World War II has had unforeseen side-effects that must now be mitigated, he fails to observe that mitigation through planning itself has deleterious consequences. For as experience in Britain,

the USSR and, indeed, America has plainly shown, the quality of decision-making almost invariably deteriorates when placed in the hands of an anonymous and inflated state bureaucracy (which is what always develops from 'planning'); and the institution of planning, whether effective or not, is only ever achieved at the expense of freedoms. The cure may or may not be worse than the disease, but it needs more discussion than Cloud seems to suppose.

Even so, *Cosmos, Earth, and Man* is precisely the sort of book intelligent students and laymen should be reading. If everyone agreed with everything in it, it would probably be dull. Preston Cloud is never that. □

Peter J. Smith is Reader in Earth Sciences at the Open University, Milton Keynes, UK.

Evocative of Dirac

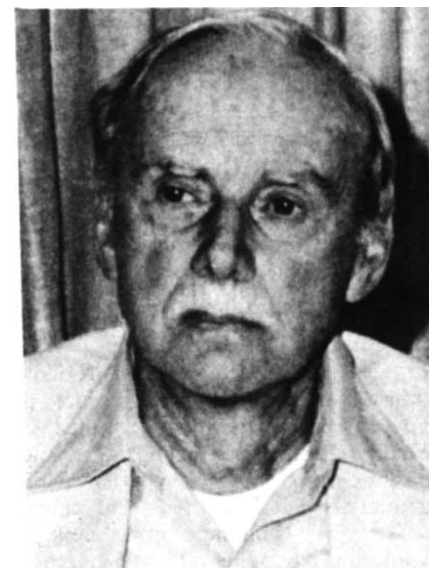
R. H. Dalitz

Directions in Physics. By P. A. M. Dirac. Edited by H. Hora and J. R. Shepanski, with foreword by Sir Mark Oliphant. Pp. 95. (Wiley: New York and London, 1978.) \$16.45; £9.20.

THE editors of this book are to be congratulated on their initiative in persuading Professor Dirac, now retired from the Lucasian Chair at Cambridge and resident at Florida State University, Tallahassee, to make a lecture tour of Australia and New Zealand in 1975, and on their decision to record and publish these lectures.

The printed lectures are very evocative of Dirac. As one reads, one soon hears in one's mind the well-measured tones of Dirac's lecturing style. They capture precisely his simplicity of statement and clarity of logic. The lectures range quite widely in topic. The first lecture, "The Development of Quantum Mechanics", is primarily historical, and of particular interest concerning the precise steps of thought in the early development of non-relativistic quantum mechanics, as Dirac joined in following the initial ideas of matrix mechanics as put forward by Heisenberg.

The second lecture, on "Quantum Electrodynamics", is concerned with second quantisation, the particle representation corresponding to a wave field, and the field-theoretic formulation of the Hamiltonian for a system of charged particles. With relativistic quantum mechanics this leads Dirac to the prescriptions of renormalisation for



Dirac in 1978

dealing with the problem of divergent integrals in the perturbation calculation of quantum electrodynamic processes. Dirac is unwilling to accept the conventional renormalisation philosophy and feels that there is a change needed in the theory, "just about as drastic as the passage from the Bohr orbit theory to the quantum mechanics".

The other three lectures are more speculative. "Magnetic Monopoles" is a topic which Professor Dirac has found attractive from quite early times. Its discussion led him to his well-known result that magnetic monopoles, if they exist, should have a quantised strength, with magnitude given by the formula $n(hc/2e)$, where e denotes the unit of charge and n is an integer. In this lecture, Dirac gave attention to the question of how these magnetic monopoles might appear in experiment; and since the lecture took place soon after the publication of a cosmic ray investigation at Berkeley which claimed

to show evidence for the existence of a magnetic monopole, it was natural for him to discuss this evidence. The lecture almost coincided with the cogent criticisms made by Professor Alvarez of this interpretation of the Berkeley evidence. Dirac has, somewhat unwisely, added an appendix to this lecture, stating that the alternative interpretation by Alvarez is now disproved; in fact, Alvarez's interpretation still stands as a possibility, as does the interpretation given here by Dirac. In this situation few physicists today believe that this event gives any appreciable support for the existence of magnetic monopoles. As Dirac says, "one very much hopes that further examples will be discovered in future experiments", for that is the only way the matter can be settled.

The fourth lecture, on "A Positive-Energy Relativistic Wave Equation", is relatively technical, being concerned with a generalisation of the equation Majorana proposed in 1937 for neutral, massless fermions. This new equation finds serious difficulties when any attempt is made to extend it to the case of a charged particle; Dirac's conclusion is that the particles must be neutral or else the equation modified. The fifth and final lecture, "Cosmology and the Gravitational Constant", is based on Dirac's *Large Numbers Hypothesis*, that the very large dimensionless numbers occurring in our description of the Universe should be related with one another. Dirac focuses attention on three such numbers, (e^2/Gm_em_p) , $(m_e c^3/te^2)$ and $\sqrt{(M/m_p)}$, where G is the gravitational constant, M the mass of the Universe and t its age. Each of these numbers is at present of order 10^{39} . Dirac concludes that, in atomic units, G and M must vary with the age of the Universe, in particular that there must be a continuous creation of matter going on, a process which may be either evenly distributed over all of space or concentrated where there is already mass. The various possibilities can be distinguished by experiment, as Dirac points out, and he surveys the status of such experiments to date, leaving us with the hope that the question may become settled within a few years. This lecture is particularly interesting in the way it illustrates the simple and logical steps which Dirac's mind follows in his development of questions in physics.

These lectures have permanent value partly for historical reasons and partly because of the picture they give of the man. The lectures impinge on a number of interesting questions, for example, the relationship of Dirac's development of quantum mechanics with the ideas of Heisenberg. They give the reason (p16) for his proposal that the negative energy solution for the

electron might have been a representation of the proton. His firm belief that physics should follow "standard mathematics" is expressed very strongly in these lectures, and brings him to the point (p36) where he is willing to give up special relativity rather than accept renormalisation. One finds this a somewhat strange opinion from the man who, after all, introduced the δ -function into physics at a time when it was mathematically disreputable. The picture which he gives of the early days of quantum mechanics is most interesting, and there is one especially quotable remark, namely that "it was very easy in those

days for any second-rate physicist to do first-rate work . . . It is very difficult now for a first-rate physicist to do second-rate work". While accepting the latter proposition, we may remain somewhat sceptical about the former.

This book of lectures goes beyond history, although already interesting for that reason, and gives us also an interesting picture of Professor Dirac's ideas of recent years. Altogether, the book is very stimulating to read and deserves a place in every science library. □

R. H. Dalitz is Royal Society Research Professor in the Department of Theoretical Physics at the University of Oxford, UK.

From quarks via tokamaks, to quasars

P. T. Matthews

A Perspective of Physics. Vol. 2. Selections from 1977 Comments on Modern Physics. Introduced by Rudolf Peierls. (Gordon and Breach: London, New York and Paris, 1978.) £16.70.

Up to the outbreak of World War II the physicists who had discovered quantum mechanics and were engaged in developing its exciting implications in nuclear, atomic, molecular and solid-state physics and astrophysics, formed a close-knit international group, small enough for each individual to follow in some detail the activities of the whole. When work on basic physics started up again after the War, it was in much the same spirit; and it was not unreasonable to attempt to keep pace with the published literature as it appeared. This did not last long. The search for fundamentals led to a whole new international community of high energy, or elementary particle physicists, working in the newly discovered sub-nuclear domain, while each of the separate areas mentioned above developed into a major field of operation with its private army of specialists communicating within its own boundaries through an ever increasing flood of specialised literature.

The pace got hotter and by the mid-1950s the published literature became largely irrelevant because it took too long for an important advance to appear in print. Research groups working on related topics all over the world, but particularly in Western Europe and America, started communicating with each other by exchange of pre-prints and conference

reports. This scientific samisdat, even within a discipline such as high energy physics, tended to produce a fragmentation into subgroups very well informed within their own narrow speciality but increasingly isolated from each other. In 1967 *Comments on Nuclear and Particle Physics* was founded in a deliberate effort to counteract this trend. In the foreword to the opening volume it is explained that a group of distinguished physicists will each be asked "to comment on work that seems to him interesting and important" in the hope that new ideas would be made available "not only to specialists in the field, but also to colleagues working in related and unrelated areas of physics". Other issues in other fields followed and although the appearance of *Comments* did not change the face of physics, there is no doubt that over the years it has helped to break down the barriers of overspecialisation.

The volume under review is the second in an annual series which takes this process one stage further. It consists of a selection of reprints of some 25 articles which have appeared in

Comments on Modern Physics during 1977. The selection has been made by Sir Rudolph Peierls. The articles are split fairly evenly under the five main headings of nuclear and particle physics, solid-state, astrophysics, atomic and molecular and finally plasma physics. The selection is preceded by an introduction written by Sir Rudolph which straddles the whole field and so puts the individual articles into some coherent context. As the blurb on the dust cover rather grandly says, the whole is an attempt "to keep both the specialist reader and interested observer abreast of the most significant developments in all modern physics".

This is a very ambitious project which probably succeeds as well as could be expected, almost exclusively as a result of Peierls' masterly introduction. Without it the collected reprints would be a jumble of fragments which would add up to very little indeed. In 25 pages, which are commendably free from specialist jargon which so often obscures such articles, Peierls gives a broad brush account of the whole background which places each of the separate papers in an intelligible relation to the rest. The fact that this is done by someone already some years past official retirement, demonstrates by example that physics is still a coherent whole, and that one man prepared to make the effort can still see it as such and can follow its major developments all the way from quarks, via tokamaks, to quasars. □

Professor P. T. Matthews was Head of the Department of Physics, Blackett Laboratory, Imperial College, from 1971-76, and is now Vice-Chancellor of the University of Bath, UK.

Mechanism of organic evolution

Evolution. By C. Patterson. Pp. 197. (Routledge and Kegan Paul, in association with the British Museum (Natural History): London, 1978.) Hardback £5.95; paperback £2.95.

At the time of the Fifteenth International Congress of Zoology in 1958, the Natural History Museum in South Kensington, London, under Sir Gavin de Beer mounted a "permanent" evolution exhibit in the Main Hall of the Museum to commemorate in part the paper by Darwin and Wallace "On the Tendency of Species to form Varieties; and on the Perpetuation of Varieties

and Species by Natural Means of Selection", read at a meeting of the Linnean Society in London on 1st July 1858. To accompany the Exhibition, the Museum published *A Handbook on Evolution*, consisting of a general essay on natural selection and a guide to the exhibits. This *Handbook* was used by generations of students.

Twenty years later, the evolution exhibit has gone and the 1958 *Handbook* now seems very superficial. We are promised a new exhibit at the Museum in due course but in the meantime the Museum's Trustees (in association with Routledge and Kegan Paul) have produced a really excellent small book on *Evolution* by Colin Patterson, who works on fossil fish at the Museum. This is a completely new book which describes and summarises

the process and mechanism of organic evolution independently of any Museum exhibits. Dr Patterson is splendidly eclectic and suitably acerbic in his reviews of the concepts and controversies that contribute to our present understanding of the diversity of life.

As is proper for a taxonomist, Dr Patterson begins with a discussion of the idea of species; and as is proper for a palaeontologist, his concept of a species is three-dimensional (based on "community of descent" rather than "community of resemblance"), and includes the reality of intraspecific variation and differentiation. This leads him on to three chapters on basic genetics, and a further three on ecological and population genetics, culminating in a description of the origin of species—the subject which Darwin did not cover in his book on the *Origin of Species*; and then to a description of speciation in the Galapagos Islands. The last third of the book contains chapters on evolution beyond the species level, proof and disproof (in which Patterson largely discounts the Popperian view that evolution is metaphysics rather than science), the origin and early evolution of life, evolution and man (sadly playing down de Beer's arguments about neoteny in favour of regulatory genes, which amount to the same thing but are much more difficult to visualise), and a Who's Who of significant evolutionists (largely illustrated with portraits from the Linnean Society's collection).

The writing is concise but clear. I can think of no other book more suitable as a general introduction to the field of evolution as a whole, or for pre-university examinations in particular. There is a brief list of "further reading" which will be a useful guide to librarians.

Patterson steers a careful course through the minefield of evolutionary controversy; one of his reasons for claiming evolution is scientific is that the debates and progress pertinent to evolution have been about a series of specific questions—the relationship between ontogeny and phylogeny, the nature of particulate inheritance, the population genetics revolution in the 1930s, DNA in the 1950s and most recently the neutralist/selectionist argument. He skirts round the clade and grade dissension which is currently raising the temperature of systematists (*Nature*, 276, 759-60; 1978). Perhaps the only area in which Patterson is not entirely fair is in the relationship between evolution and Christianity; and he is hardly to be blamed because of the ability with which Christians from Soapy Sammy Wilberforce onwards have obfuscated their position.

The problem about evolution for Christians is that it seems on the surface to dispose of the need for a creator. The naive solutions are in Patterson's words:

"at one extreme the fundamentalist view that evidence of evolution, such as fossils, was built into the newly-created rocks to tempt us or test our faith. At the other extreme is the person to whom evidence of evolution only pushes the activity of the Creator further and further into the past. Both these modifications of the original creation myths are typical evasive moves, avoiding refutation or confrontation by modifying the original theory or erecting subsidiary defensive theories around it". True, and Patterson comes close to

a positive approach to the old dispute when he points out that it is equally "depressing to be . . . a pointless experiment in protein chemistry or an experiment in ethics, which is the Christian message read from the same nihilist or 'nothing but' viewpoint".

The logical fallacy of 'nothing but-tery' has been recognised at least since the time of Aristotle; the fact that the same event may have more than one cause ought to have been assimilated by now—by both scientific reductionists and religious simplifiers.

R. J. Berry

R. J. Berry is Professor of Genetics at University College, London, UK.

Appealing astronomy

Beyond the Moon? Written and presented by Simon Mitton. (ATV: London, 1979.) First programme transmitted in the UK: 09.10. 21 April, on ATV (Midlands). Other channels: morning, 22 April, 1979.

IN view of its position as the most 'popular' of the physical sciences, astronomy has all too little television time allocated to it. ATV is therefore to be congratulated on running a seven-part introductory series, "both for those who are interested in the subject—and those who think they might be." In each programme Simon Mitton, as both writer and presenter, takes up a different strand and develops it from the historical point of view within a loose framework, which begins traditionally enough with the planets, and extends to encompass the stars, life in the Universe, interstellar travel, and the "far future".

The historical aspects are enlivened with biographical details which paint astronomers as real people; one appealing sequence was the summary of Newton's achievements in terms of the illustration on the current £1 notes. Despite Mitton's breathless enthusiasm, however, the production is too often constrained by a rigid studio format: presenter at desk with TV monitor. The programmes impress most through their studio demonstrations and film sequences. Demonstrations in the planetary programme range from antique orreries to a water bath for floating models of the low-density giant planets. Some of the demonstrations are unfortunately impressive at the expense of basic physics: the buoyancy of a helium balloon in air is adduced as evidence that the Earth's gravity is incapable of retaining helium atoms, and in a comparison of the weights of model gas molecules helium is represented as He₂. One surprisingly successful de-

monstration was a simple scale model of the Sun, Earth and Moon, that conveyed powerfully their relative sizes and distances, and the general emptiness of interplanetary space.

Film sequences from the Royal Greenwich Observatory and the Cambridge Institute of Astronomy provide strong links with the realities of observational astronomy. For example, the opening programme, though perhaps biased to the possibilities open to amateurs at the expense of the excitement of current research, is imaginatively set within the dome of the Isaac Newton Telescope; and in a later sequence, Mitton recounts the story of the discovery of Neptune from the dome of the Northumberland telescope, the instrument with which Challis almost forestalled Galle's identification of this new planet.

Although the series is carefully thought-out, the programmes seem to suffer from the limits on air-time and budget-restrictions: for example, the animations are crude, and some of the studio and film shots should have been retaken. Among the latter are some shots where slips of the tongue have unfortunately been allowed to survive: a light year is described as "10 million million miles" (rather than kilometres), and Jupiter's 'year' as 13 yr (instead of 11.9 yr), to take just two early examples. In addition, some viewers may find Mitton's presentation slightly patronising. To take one example, a description of 8×30 binoculars as "suitable for sport, and all right for ladies to do astronomy" will not be popular in some quarters. And a half-hour programme without interviews, and with only one presenter, can seem very long. Still, astronomy is an exciting subject, and Mitton's enthusiastic presentation is likely to convince even the casual viewer that astronomy is a subject he should learn more about.

Nigel Henbest

Nigel Henbest, formerly a researcher in radio astronomy, is now a freelance journalist.

obituary

Ralph A. Sawyer

RALPH ALANSON SAWYER, physicist and science administrator, died on 5 December 1978 at the age of 83.

Born in New Hampshire, he graduated valedictorian of his class from Dartmouth College in 1915 and then went to the University of Chicago on a travelling fellowship as a Chamberlain Fellow from Dartmouth. At Chicago he became one of R. A. Millikan's students and, after a brief tour in the US Navy, he received a PhD degree in physics there in 1919. Soon afterward Ralph joined the staff of the physics department at the University of Michigan and, except for the years of World War II, he served the University as a prolific researcher, dedicated teacher and, later, as a gifted administrator until his retirement in 1964.

Before he was called back into active service by the Navy in 1942 Ralph had published more than 50 papers in the field of spectroscopy. His interest in the spectra produced by energetic light sources, which began with his first publication at Chicago on the characteristics of a vacuum spark, continued into his earlier years at Michigan. Using a normal-incidence vacuum spectrograph of his own design, together with an improved hollow-cathode light source, for the extreme ultraviolet, Ralph and his students analysed the first spark spectrum of a considerable number of elements.

In the mid-thirties he became interested in rapid quantitative spectrochemical analysis and together with H. B. Vincent he developed the techniques to the point where a technician could make 'on line' determinations of the composition of samples in the steel-making process fast enough to control the composition of the batch of metal being processed.

From 1942 to 1945, on leave from the University, Sawyer served as Director of the Armor and Projectile Laboratory at the Naval Proving Ground at Dahlgren, Virginia. However, he still maintained an active interest in spectroscopy and managed to finish his book *Experimental Spectroscopy* which was published by Prentice-Hall in 1944 and then, in revised form, in 1951. A third, paperback, edition was published by Dover in 1963.

In 1946 Sawyer was appointed Civilian Director of Technical Operations for the series of atomic bomb tests at Bikini Atoll known as 'Opera-

tion Crossroads'. In view of the fact that he was both a Naval officer and an eminent scientist of proven administrative ability this was an ideal choice. The successful completion of this mission marked the end of Ralph's active service to the Navy and he was awarded their Commendation Ribbon. Later (1951) he was promoted from the rank of Commander to that of Captain in the Naval Reserve.

While the Bikini tests were in progress Sawyer was notified of his appointment as Dean of the Graduate School at Michigan and in the fall returned to Ann Arbor to assume the position which he held until his retirement.

Ralph's talent for administration brought him additional responsibilities. He became the first director of the Michigan Memorial Phoenix project which was devoted to the study of the peaceful uses of atomic energy and then, in 1959, he was appointed to the newly-created post of Vice-President for Research at the University of Michigan. These were times of new and rapidly expanding Federal support of university research and Ralph was in large measure responsible for establishing the University of Michigan as one of the leaders in Federally-sponsored research.

Amid all these activities Sawyer somehow found time for service to various off-campus organisations. He served a term as President of the Optical Society of America and, earlier, was an associate editor of their journal. In 1963 he was awarded the Frederic Ives medal by the Optical Society for 'distinguished work in optics'. Ralph was elected to the Governing Board of the American Institute of Physics in 1954 and served as its chairman from 1959 to 1971. This was a period in which many hard decisions had to be made and Ralph was described by one of the board members as a 'benevolent but firm leader, deeply respected by all'. Upon his retirement from the chairmanship he was awarded the Karl Taylor Compton gold medal by the Institute for 'distinguished statesmanship in science'. Sawyer also served a term as President of the Association of Graduate Schools and was advisor to or member of: the National Research Council, the Goddard Space Flight Centre, the National Bureau of Standards, the International Commission on Optics, and three US Naval Laboratories.

It can truly be said of Ralph Sawyer

that 'he lived a life of large usefulness'. Those of us who knew him well will miss his warm friendship and the entire scientific community will mourn the loss of his leadership.

W. Wallace McCormick

D. I. Blokhintsev

DMITRII IVANOVICH BLOKHINTSEV, the founder of the Soviet nuclear power industry and a prominent theoretical physicist, died suddenly on 27 January 1979. Although 71 years old, he was still actively involved in teaching at Moscow State University—his own alma mater—and in his work as head of the Laboratory of Theoretical Physics at the Joint Nuclear Research Institute at Dubna.

Blokhintsev had formerly been director of the Dubna Institute, from its foundation in 1956, until his official retirement in 1965. It was here that, in 1964, he announced the synthesis of element number 104. The Dubna institute was one of the first major joint efforts of the socialist bloc—the Comecon countries, with the addition of China, North Korea, North Vietnam, and Albania. As Director of the Institute, Blokhintsev received a number of orders and medals from the countries involved, as well as election to several foreign Academies.

Soviet honours, too, were bestowed on him, including the title of Hero of Socialist Labour, the Order of Lenin (four times), the Order of the Red Banner of Labour, the Order of the October Revolution and the Lenin and Stalin (now State) prizes. Many of these awards, including the Lenin Prize, were associated not so much with his academic talents but with his expertise as an organiser of the Soviet Union's nuclear power programme. In 1954, he was in charge of the construction of the Soviet Union's first nuclear power station, a modest 5,000 kW 'semi-pilot' plant at Obninsk, which was to do much, in the following decade, towards the development of Obninsk as a scientific centre with a wide range of research institutes.

Nevertheless, Blokhintsev's achievements in pure physics did not go unnoticed at home. Indeed, in the official *Pravda* obituary, which was signed by numerous high-ranking officials, including Messrs Brezhnev and Kosygin, pride of place is given to these. In the words of this official appreciation 'he enriched world science by his fundamental works in the field of quantum

theory, solid-state semiconductor physics, acoustics of inhomogeneous media, quantum mechanics, the theory of chain reactions in atomic reactors, and the physics of elementary particles. His death, it says, is a serious loss to Soviet science.

Vera Rich

Peter Bishop

DR PETER MAXWELL FARROW BISHOP, FRCP (Lond.), FRCOG, one of the pioneers of British clinical endocrinology, died on 19 January 1979 at the age of 74. His main achievements were in gynaecological endocrinology, of which he was the prime mover in the United Kingdom.

He was born on 14 August 1904, the son of a doctor, and was educated in Berlin and at Charterhouse, Trinity College, Oxford and Guy's Hospital Medical School, from which he qualified in 1929.

He entered the clinical field from the physiology laboratory at Guy's Hospital Medical School, where he was demonstrator and lecturer from 1930 onwards and where his researches included the modification and application of the Friedman test for pregnancy. With the help of a physician and in liaison with the gynaecological department, he started an endocrine clinic for functional menstrual disorders in 1934. He studied the effects of oestrone in amenorrhoeic women and of the new corpus luteum extract (progesterone), soon replaced by synthetic progesterone, in dysfunctional uterine bleeding and recurrent abortion. The clinic later expanded to include testicular and other endocrine disorders.

He was quick to recognise the clinical applications of recent animal experiments and was in close touch with new developments in the pharmaceutical field. Thus he applied the concept of the oestrogen threshold for uterine bleeding developed by Zuckerman in primates and, following the experiments of A. S. Parkes and his colleagues in rats, he was the first to demonstrate the effectiveness of crystalline oestrone implanted subcutaneously in a human female castrate. At the request of the Therapeutic Trials Committee of the Medical Research Council, he undertook the first clinical trial of the earliest synthetic oestrogen, diethylstilboestrol, synthesised by E. C. Dodds and his colleagues in 1938.

His researches were interrupted by the Second World War, during which he was preoccupied with administrative duties at the hospital, although he continued his clinical work and studied with S. J. Folley the rates of absorption of various hormones from subcutaneously implanted pellets.

After the war he was appointed Consultant Endocrinologist to Guy's Hospital and Chelsea Hospital for Women and Senior Lecturer in the Obstetric Department at The Royal Postgraduate Medical School. At Chelsea he made painstaking studies of the comparative potencies of various synthetic oestrogens, as determined by the dosage required to induce withdrawal bleeding in amenorrhoeic women. He also published further studies of the use of implanted progesterone in women with recurrent abortion. At the same time, with his gynaecological colleagues at Chelsea, he established a clinic for the investigation and management of infertility. He also took part in the first British clinical trials of ACTH and cortisone in rheumatoid arthritis in 1950. In later years he and his colleagues were involved in a variety of publications, including the use of dydrogesterone in dysmenorrhoea, induction of ovulation with clomiphene, the use of oral contraceptives, genetic studies in gonadal dysgenesis and the management of Cushing's syndrome.

He was a fine teacher and excelled in his lectures on various endocrine topics and clinical demonstrations of endocrine disorders. Not only undergraduate students but many young physicians and gynaecologists, both at home and from overseas, gained their knowledge and experience of endocrinology under his guidance. His writings were extensive, lucid and stylish. Apart from his original articles he wrote monographs on gynaecological endocrinology and on the chemistry of the sex hormones. He also wrote single-handed the 7th edition of *Recent Advances in Endocrinology* (1954) and contributed numerous chapters to other textbooks and invited articles to various journals for the general reader.

He was at various times President of the Section of Endocrinology of the Royal Society of Medicine and Chairman of the Society for the Study of Fertility and of the Council of Management of the *Journal of Reproduction and Fertility*. He was also Medical Consultant to the Family Planning Association.

Dr Bishop had the unusual distinction of being elected Fellow of both The Royal College of Physicians and The Royal College of Obstetricians and Gynaecologists. He was Sir Arthur Sims' Travelling Professor in 1964. In the year of his retirement from hospital in 1969 he became Master of the Society of Apothecaries.

He retained single-minded dedication to clinical endocrinology throughout his career despite considerable scepticism and opposition from others. This required great determination and

courage: qualities which he likewise displayed in the face of the physical disability which followed his retirement and immobilised him for the last few years of his life, but which never extinguished his interest in his subject nor his zest for living.

Robert R. de Mowbray

Fred Lang

THE death of Dr Fred Lang at the age of 34 in an automobile accident on 8 December 1978, cut short a promising career in neurobiology. He was Associate Professor of Biology in Boston University; he taught in the Boston University Marine Program at Woods Hole, Mass., and was a director of the winter neurobiology course given there. Recently he had received a Career Development Award from NIH to further his research on invertebrate neuromuscular systems, which had reached a flourishing stage and had attracted a large entourage of graduate students at Woods Hole.

Fred Lang worked as a graduate student with Bernard Abbott and Ladd Prosser at the University of Illinois, and as a postdoctoral fellow with Harold Atwood at the University of Toronto. His initial work on the innervation of the heart of the horseshoe crab *Limulus*, and on neuromuscular physiology of crustacean limbs, was extended later to include development of neuromuscular synapses in crustaceans, and in particular, development of the nervous system and muscles in the American lobster, *Homarus*. He and his collaborators described the physiological properties of the differentiated asymmetric 'crusher' and 'cutter' claws of the lobster, and then looked for neural and environmental influences on differentiation. In addition, adaptation of the animal to its environment was examined. A thorough description of physiological and morphological changes occurring in the muscle fibres throughout development led to a correlation of muscle fibre properties with their innervation and to a demonstration that muscle differentiation could be influenced by conditions in the animal's environment. Although this evidence suggests a neural influence on muscle differentiation, the problem remains open and controversial.

His enthusiastic activity, his lively and forthright dialogue, and his ability to generate interest and debate, will be well remembered. He had an important place among invertebrate neurobiologists.

H. L. Atwood